RESPONSE ADAPTIVE DESIGNS FOR HIGHLY SUCCESSFUL TREATMENTS, RANDOMNESS AND RELATIONSHIP DETECTION IN CLINICAL TRIALS

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ABSTRACT

Steven Hoberman: Response Adaptive Designs for Highly Successful Treatments, Randomness, and Relationship Detection in Clinical Trials
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In the first part of our research we consider a problem of reducing the expected number of treatment failures (a binary response indicator) in trials where the probability of response to treatment is close to 1 and treatments are compared based on log odds ratio. We propose a new class of urn designs for randomization of patients in a clinical trial. The new urn designs target a number of allocation proportions including the allocation proportion that yields the same power as equal allocation but significantly less expected treatment failures. The new designs are compared with the doubly adaptively biased coin design, the efficient randomized adaptive design and with equal allocation. The properties of the new class of designs are studied by embedding them into a family of continuous time stochastic processes.

In the second part of our research we study entropy as a measure of randomness in a clinical trial. For any randomization design we define a sequence of probability distributions. We then use this sequence to formulate and prove a statement about conditions for the asymptotic mean entropy of a randomization design to achieve its maximum value. We compare randomization designs and response adaptive randomization designs with respect to the asymptotic mean entropy. We derive a relationship between the limiting variance of distributions in the sequence to the mean entropy under a normality condition and apply this result to the doubly adaptive biased coin design.

We develop two new methods of imputation for survival data that allow for application of the Brownian Distance Covariance. We use these two methods with survival data that have different levels of censoring, and different relationships that are not all easily detected by the Cox model. These methods are also compared to a relationship detection technique developed by Kwak for censored data.

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CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

The clinical trial has long history in biostatistics. One of the most important issues in clinical trials is how to assign patients to different treatments. One of the first ways proposed to do this is simple randomization. This method involves flipping a coin with a certain success probability and assigning patients to one of two treatments depending on the result of the coin flip. The problem with this approach is that it can lead to imbalances in the number of patients assigned to each treatment that can affect power. One way statisticians have sought to deal with this issue is to create more complex treatment assignment regimes that depended on the trial assignments previous to the current patient. There are many attractive features of such schemes, but one major drawback is that they introduce the possibility for new kinds of bias to enter the trial.

Statisticians conducting clinical trials have long sought ways to mitigate this bias. As early as the 1960's, designs for equal treatment allocations and their possibilities for bias were discussed (Stigler, 1969). This was in the case where the total number of patients was fixed. It was mentioned that the truncated binomial design was minimax for bias in the case where there were two levels of bias, $\mu - d$ and $\mu + d$. Here μ is the mean effect of the treatment and d is a positive real number indicating bias. The author mentions that even under minimaxity the bias does not approach zero asymptotically because the scaling factors cancel. This leads to the introduction of a random allocation design, where patients are assigned to treatments by flipping a biased coin whose bias depends on the history of the treatment allocation in the trial. Stigler

showed that this Bayesian design, which minimizes the Bayes risk of the experimenter's strategy. However, this result depended on the simplicity of the two level distribution of bias known to the investigator.

Efron suggested an allocation scheme that involved flipping a fair coin if the allocation to each treatment was equal, and flipping a bias coin with bias towards the less frequent treatment if there was imbalance (Efron, 1971). In this scheme, the number of patients in the trial was unbounded. He referred to covariate bias as accidental bias. This is the bias that results from random differences in covariate values in the patient population. Selection bias, which is also important, is defined as the bias that results from the baseline characteristics of the patients assigned to each treatment differing due to knowledge that the investigator has about the previous patients or (Blackwell and Hodges, 1957).

Efron also introduced an early method to replace the coin flip as a treatment allocation scheme. It is called Efron's coin (Efron, 1971). The idea is that if the number of patients assigned to each treatment is equal then a fair coin is flipped to determine the next treatment assignment; if there is an imbalance, then a biased coin with probability $p > 0.5$ is flipped, and if the coin lands heads, then the next patient is selected to decrease the imbalance. The value of p may vary.

Efron mentioned that the "best" guessing strategy at patient n, if the treatments were unmasked and the goal is to guess the next treatment assignment, was to guess the treatment that appeared least often (Efron, 1971). This yielded an asymptotic probability of correctly guessing the next treatment as $0.5+(r-1)/4r$, which implies excess selection bias of $(r-1)/4r$. Here $r = p/(1-p)$. There is an explicit form for the excess selection bias (Markarayan and Rosenberger, 2010). Efron did not cover a scenario for a coin targeting an allocation different from 0.5.

Accidental bias is quantified as being $\boldsymbol{z}'\Sigma_{T_n}\boldsymbol{z}$, where Σ_{T_n} is the covariance matrix of the treatment vector and $\boldsymbol{z}$ is the covariate vector (Efron, 1971). Recently a compact form for this matrix was discovered (Markaryan and Rosenberger, 2010). This bias must be less than the maximum eigenvalue of Σ_{T_n} (Efron, 1971), and the upper bound was recently sharpened (Markaryan and Rosenberger, 2010).

The goal of response adaptive designs is to change allocation away from equal allocation in order to assign more patients to the better treatment or to reduce the variance of the estimated treatment effect or both. One early example of this is the play-the-winner rule. It's first incarnation, (Zelen, 1969), involved switching treatments after a failure on the current treatment is observed. The randomized play the winner rule, (Wei, 1978), involves an urn containing two different colors of balls. Each time there is a success on a certain treatment, a ball of the corresponding color is added to the urn. If there is a failure on that treatment, the opposite color of ball is added to the urn. The next treatment is assigned by choosing a ball at random from the urn. Both play-the winner rules target the same allocation of $q_2/(q_1 + q_2)$ where q_i is the failure probability of treatment i. However, the allocation that both of these treatment allocation strategies target is fixed and may not yield optimal power. The average power in a clinical trial is a decreasing function of the variability of the allocation proportion (Hu and Rosenberger, 2003). Also, researchers desired allocation schemes that were more flexible about the allocation they targeted. It is this scenario that motivated the development of the doubly adaptive biased coin (DABC), (Hu and Zhang, 2004).

The doubly adaptive biased coin chooses the next treatment with probability:

$$g(x,\rho) = \frac{\rho(\rho/x)^{\gamma}}{\rho(\rho/x)^{\gamma} + (1-\rho)\left[(1-\rho)/(1-x)\right]^{\gamma}},$$
$$g(0,\rho) = 1,$$
$$g(1,\rho) = 0.$$

Where ρ is the estimated target allocation for treatment 1, x is the actual target allocation for treatment 1, and γ is a nonnegative randomization parameter that is constant throughout the trial (Hu and Zhang, 2004).

Hu and Zhang show a law of the iterated logarithm of the doubly adaptive biased coin designs as well as several other designs (Wei, 1978). A law of the iterated logarithm is a standardization of the sum of a sequence of random variables that converges in probability but not almost surely. By using martingale methods and the law of the iterated logarithm, they prove asymptotic normality of allocation proportions under some general conditions. This law is used to show asymptotic normality of the allocation proportion of the doubly adaptive biased coin (Hu and Zhang, 2004). Joint bivariate normality of the allocation proportion and target allocation are also shown upon standardization by $\sqrt{n}$. The values in the covariance matrix for the multivariate normal distribution are determined by the same methods.

The doubly adaptive biased coin can be used for either continuous or binary outcomes. The variance of the allocation proportion for the doubly adaptive biased coin is smaller than that for the randomized play the winner rule, especially when the allocation proportion is close to 0.5 (Hu and Zhang, 2004).

The coin can be generalized to the case of more than two treatment groups (Hu and Zhang, 2004). They prove results about the coin when the following conditions are considered.

1) $g(v, v) = v$ and $g(x, y) - g(x, v) \dashrightarrow 0$ as $y \dashrightarrow v$ when x and y represent discrete densities

2) $g_k(x,v)$ is Lipschitz continuous with an upper bound of 1 when x is a discrete density and x_k is greater than v_k.

3) For any $0 < \delta < 1/K$ and each k in (1, ..., K), there exists a constant $c_\delta > 0$ such that $g_k(x, y)|_{x=0} \geq c_\delta$ for all x, y with $x1' = 1$, $y1' = 1$, $y \in [\delta, 1)^K$,

$$\liminf x_k \to 0^+ \frac{g_k(x,y)}{\min\{x_1,\ldots,x_k\}} > c_\delta \text{ uniformly in } x, y$$

$$\text{with } x1' = 1,\ y1' = 1,\ y \in [\delta, 1)^K.$$

It is important to understand that condition 3 exists to avoid experimental bias. If all estimated target allocations for each of the k arms are not small, but the actual allocation to treatment k is very small, the probability of assigning the next treatment to k should not be too small in order to avoid large experimental bias. The authors claim that if the greater than sign is replaced by a less than sign then condition 3 follows from condition 2 (Hu and Zhang, 2004).

If the Lipschitz continuity constant referred to in the conditions for the randomization function is less than 0.5, then the convergence of the actual allocation proportion to the vector of target allocation proportions is of order $loglog(n)/\sqrt{n}$ and the convergence of the estimated target allocation vector is also of order $loglog(n)/\sqrt{n}$ Both of these convergences are almost sure.

The asymptotic variance of the allocation proportion of the DABC is a decreasing function of the randomization exponent in the formula, regardless of the explicit form of the target allocation, as long as the conditions elaborated above are satisfied (Hu and Zhang, 2004).

Another design that was proposed after the doubly adaptive biased coin was the efficient randomized adaptive design (ERADE). This is design is a combination of Efron's coin and the doubly adaptive biased coin. Let x be the actual allocation to treatment #1 in the trial, ρ be the estimated target allocation, and α be a parameter between zero and one. The ERADE assigns the next patient to treatment #1 with probability:

$$\alpha\rho \quad \text{if } x > \rho,$$

$$\rho \quad \text{if } x = \rho,$$

$$1 - (1 - \alpha)\rho \quad \text{if } x < \rho.$$

When the log odds ratio, $\log[p_1 q_2 / (q_1 p_2)]$, is of interest, the allocation to treatment #1 that minimizes the asymptotic variance of the log odds ratio estimate is $\rho_1' = \sqrt{p_2 q_2} / (\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$ (Ivanova, 2003). This allocation also minimizes the sample size required to achieve given power if testing is based on the log odds ratio. The allocation that minimizes the expected number of failures for a fixed variance of the estimated odds ratio is $\rho_2' = \sqrt{p_2} / \left(\sqrt{p_1} + \sqrt{p_2}\right)$. The allocation that yields the same power as equal allocation for testing the log odds ratio is $\rho_3' = p_2 q_2 / (p_1 q_1 + p_2 q_2)$. When $\min(p_1, q_1) \le \min(p_2, q_2)$ $0.5 \le \rho_1' \le \rho_3'$ and any allocation inside the interval [0.5, ρ_3'] yields higher or the same power for testing the log odds ratio. Similarly, when $\min(p_1, q_1) \ge \min(p_2, q_2)$ $\rho_3' \le \rho_1' \le 0.5$ and any allocation inside [ρ_3',0.5] yields higher or the same power than equal allocation. It happens that $\rho_i' = 1 - \rho_i$, i = 1, 2, 3.

The Neyman allocation, $\rho_1 = \sqrt{p_1 q_1} / (\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$, maximizes the power of treatment comparison under a Z test for a $p_1 - p_2$ when the sample size is fixed. It assigns more patients to the treatment with the larger variance, while the allocation ρ_1' does the opposite. Therefore, the allocation ρ_1 is "ethical" (assigns more patients to the better treatment) when, for example, both treatments have success rates below 0.5. Let without loss of generality $p_1 \geq p_2$. When $0.5 \geq p_1 \geq p_2$ any allocation inside the interval [0.5, ρ_3] is a desirable allocation for testing H_0: $p_1 - p_2 = 0$ as it yields higher or the same power and assigns more patients to the better treatment than equal allocation. The allocation ρ_1' is "ethical" when both treatments have success rates higher than 0.5. It has been argued that response adaptive designs are most useful in trials with highly successful treatments (Ivanova and Rosenberger, 2001). Also in trials where it is most desirable to minimize the number of treatment failures, the treatment failure as often death; therefore we discuss the case of comparing treatments with $p_1 \geq p_2 \geq 0.5$ in more detail. For $p_1 \geq p_2 \geq 0.5$ any allocation inside the interval [0.5, ρ_3'] is a desirable allocation for testing the log odds ratio as it yields higher or the same power and assigns more patients to the better treatment than equal allocation.

Historically, designing an allocation scheme for a clinical trial requires balancing a number of different factors. This includes the desire to assign patients to treatment that appears superior during the course of the trial, as well as to achieve higher power with such allocations as the Neyman allocation.

An early approach to assigning patients in this way was to flip a coin with probability equal to the estimated target allocation (Melfi and Page 2001). For example, under this approach, the next patient would be assigned to treatment #1 with probability $\sqrt{\widehat{p_1 q_1}}/(\sqrt{\widehat{p_1 q_1}} + \sqrt{\widehat{p_2 q_2}})$ in

the Neyman allocation. The authors show that the allocation to treatment #1 converges almost surely to the target allocation as well under this scheme.

Some take the view that randomization not only mitigates biases but is the basis for inference, and is therefore very important (Rosenberger and Lachin, 1993). The first approach, however, introduces positive correlation between the sequential treatment allocations, which can increase the variance of the allocation proportion and therefore decrease power.

The Z test setup can be used to show that the size of the noncentrality parameter for the associated Chi squared distribution in the test corresponds to the power of the trial (Hu and Rosenberger, 2003). The authors use a power series expansion to show that the Neyman allocation maximizes this power. There are more complicated procedures that do as well, but what is necessary for these procedures to work is that the allocation proportion converge almost surely to constant.

These results are also generalized to a multi-treatment clinical trial setting where the test is an omnibus test of whether any are different from the null. The authors also use simulations to show that the urn allocation has the smallest failure rate and noncentrality parameter, a second design (with allocation probability proportional to $\sqrt{p_1/p_2}$), has the next smallest of each, followed by the Neyman allocation with the highest power and highest failure rate.

Among the response adaptive randomization procedures, Ivanova's drop the loser rule has the most power, followed by the DABC. However, it is important to remember that the DABC can target more allocations than Ivanova's rule. It has been shown that there was an asymptotic lower bound on the variability of the allocation proportion (Hu, Rosenberger and Zhang, 2006). The authors compute the lower bound by multiplying the product of the partial

derivatives of the target allocation by the inverse of the Fisher information when the target allocation is achieved. Besides Ivanova's drop the loser design, Zelen's play the winner rule also achieves this lower bound (Hu, Rosenberger and Zhang, 2006). In the proof of the main result a sequence of independent random variables is created from the original sequence via an application of the Martingale central limit theorem.

Some of the earliest statistical theory deals with trying to detect a linear relationship between a pair of random variables. However, often other relationships are of interest. Other attempts to capture these relationships statistically include CorGC (Delicado and Smrekar, 2009), mutual information (Breiman, 1968), and the Spearman rank correlation coefficient (Breiman, 1968). Mutual information is a way of assessing how close the relationship between two random variables is to independence. It is computed by taking the Kullback-Leibler divergence between the joint density and the product of the marginal densities. The Spearman correlation coefficient is based on the ranks of the data and is geared toward discovering a monotonic relationship. The CorGC is based on principal curves that are fit to the data. As with any two methods, the principal curve has drawbacks. The latter two methods make some assumptions about the relationship in the first place, while mutual information is harder to implement in smaller samples when the form of the density must itself be estimated.

In the middle of the last century (Renyi, 1959) several axioms were proposed that a measure of dependence between two random variables defined on the same probability space must have.

i) The measure should be defined for any pair of random variables (X,Y), neither of them being constant with probability 1.

ii) The measure should be symmetric

iii) It should lie within [0,1]

iv) It should equal zero only in the case of independence.

v) It should equal one only in the case of strict dependence of the two random variables.

vi) It should be invariant under functions of it two arguments that map the real line in a one to one way onto itself.

vii) If the joint distribution is bivariate normal, then the function should be equal to the absolute value of the correlation coefficient.

Later in the twentieth century several different dependence measures were proposed,, but not all of them satisfied these axioms. The CorGC satisfied axioms ii), iii), and vii), as well as curved based analogues of axioms i) and v) (Delicado and Smrekar, 2009). The method is best designed for arguments distributed along a curve with no noise. Local measures of linearity on the curve are defined and then they are aggregated to obtain global measures of dependence.

Recently a new measure of dependence of random variables was proposed that was computationally straightforward and did not require any assumptions (Sekely and Rizzo, 2009). It could be used for both multivariate and univariate data. The approach requires the ratio of the product of mean absolute differences from the different group means. The formula follows from a theorem about characteristic functions and a complex trigonometric integral that is related to the gamma function. The statistic has a well defined null distribution in the case of independence which is consistent for any alternative. It can also be derived from the covariance determined by conditioning on independent Wiener processes, hence the name. The big strength of this statistic is that can detect any relationship between two possibly multivariate random variables. However, it has drawbacks of its own. When the statistic is calculated for two different pairs of random variables, it is not clear if the two different relationship strengths can be compared. In the case of

the Pearson correlation, the comparison would indicate the strength of the linear relationship. Another potential drawback to this method is that it does not reveal the actual nature of the relationship, just that one exists.

It has also been shown on the machine learning side, that Reproducing Kernel Hilbert Space measures can be viewed as an extension of the distance covariance.

Another method to search for patterns in large data sets that was recently introduced is called the MINE statistic (Reshef, et al. 2011). This statistic also has the ability to detect arbitrary relationships in data sets. Like the Brownian distance covariance, it is invariant under affine transformations. It is also a rank statistic and it is this property that is used for computing tables of p values. The authors compare the statistic to several other statistics used to find general relationships, including the Brownian Distance Covariance. They note that it is only their statistic that has the property of equitability between different relationships with the same amount of noise. What they mean by this is that if two data sets are generated by drawing values from two different mathematical functions at random and perturbing each of them with the same amount of symmetric normal noise, then the value of the MINE statistic will be very similar for these two data sets. The statistic relies on the concepts of mutual information mentioned earlier. It statistic can be computed in a series of steps.

First, a series of different grids is drawn over the data scatterplot. The grids increase in the number of cells, and each grid is selected using a greedy algorithm. The maximum size of the grid was chosen by the authors after some empirical evidence, to be the number of data points raised to the power of 0.6. For each grid, the mutual information of the induced discrete distribution is recorded and is divided by the maximum possible value of the mutual information

for the grid, given its dimensions. This maximum can be easily derived from the theoretical formula for mutual information. The maximum of this ratio across all grids that are investigated is called the MIC. A MINE statistic is a statistic that's based on the MIC. These include ways to assess degrees of monotonicity or closeness to being a function. A larger MIC indicates a stronger relationship, and the grid that is retained from the calculation offer insight into what the explicit relationship is, which the Brownian distance covariance does not.

The MIC has certain desirable properties. First, in the case of statistical independence, it converges to zero in probability. Second, in the case of statistical dependence the statistic is bounded away from zero almost surely. Third, if the data are drawn from a noiseless functional relationship then the MIC converges to one. A property noticeably missing from this list is consistency: the authors do not show that the MIC converges to a number between zero and one in the case of noisy dependence. The Brownian Distance Covariance statistic, however, does have the property that it converges to its theoretical value in large samples. It has also been argued that the MINE statistic suffers from low power when the sample size is reasonable (200-300) (Gorfine-Orgad, 2012). Kosorok (personal communication) also observed that the MINE can register sizable correlations for random noise in reasonable samples, suggesting that Type 1 error may also be a problem in those samples as well. The MINE statistic is also not precisely equitable; it is a property that is established through simulation studies that are compare MINE to other methods.

One issue that is related to both the Brownian Distance Covariance and the MINE statistic is whether information about a change in the marginal mean of one variable with respect to the second can be extracted from information about the existence of a relationship. The same

can be said of the marginal variance. In survival analysis these questions are often more of interest than simply whether a relationship exists.

The literature reveals several different issues that are longstanding in the statistical community. One of these is the attempts to minimize selection bias as well as other kinds of bias. Selection bias has been studied in allocation regimes that have a fixed target allocation and those that do not. However, one important question that until now remains unanswered is, what is the minimum amount of selection bias that one may have in a clinical trial with an arbitrary target allocation? This is one of the questions that we address with our research. An issue raised by higher order urn models is in what circumstances they would outperform methods such as DABC and ERADE in terms of power and resistance to selection bias. That is an issue that we are able to address. Another question that is raised by methods related to detecting nonlinear relationships is whether these methods can be adapted to censored data that is found in survival analysis. That is also one of the questions that we address. Also, it is important to consider the modification of new relationship detection methods to search for relationships between several different random variables. Another issue that is not addressed in the literature is what can be said about the distance covariance or MINE statistic between a pair of random variables given that the corresponding statistic between each random variable and a third random variable is already known.

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CHAPTER 2: HIGHER ORDER RESPONSE ADAPTIVE URN DESIGNS FOR HIGHLY SUCCESSFUL TREATMENTS

2.1 Introduction

Consider the problem of comparing two treatments in a randomized clinical trial. An issue that is central to such a trial is balancing the ethical imperative to assign more patients to the better treatment with the need to have sufficient power to compare the treatments. Response adaptive designs change allocation away from equal allocation based on responses observed so far in the trial; see Hu and Ivanova, 2004, and Hu and Rosenberger, 2006, for review. Early response adaptive designs, generalized Pólya urn (Athreya and Karlin 1968; Zhang et a., 2006), the play-the-winner rule (Zelen, 1969) and the randomized play the winner rule (Wei and Durham, 1978) were developed for comparing treatments with binary outcomes to yield "ethical" allocation in the limit, that is, to assign more patients to the better treatment. Their limiting allocation, as well as the limiting allocation for the urn design of Ivanova (2003), though "ethical", is not optimal with respect to maximizing power of the treatment comparison. In some cases, a trial with allocation proportion that is not optimal in terms of power requires many more subjects to achieve the same power than equal allocation. This can result in observing more failures in the trial than under equal allocation, therefore defeating the purpose of a response adaptive design to reduce the average number of failures in the trial. Other response adaptive designs such as doubly adaptive biased coin designs (Eisele, 1994; Hu and Zhang, 2004), and the efficient randomized adaptive design (ERADE) (Hu, Zhang and He, 2009) can target any

desired allocation including the allocation that maximizes power.

An important metric of any allocation procedure is the amount of randomness it provides. In a deterministic procedure the next assignment can be predicted for sure if all previous assignments and outcomes, in case of response adaptive allocation, are known. On the other side of a spectrum is a fully randomized allocation procedure, an allocation via a fair coin, in case of equal allocation, or biased coin otherwise. We use entropy to measure randomness of the designs, a measure that has not been used before when response adaptive designs were compared. This allows making a fair comparison of adaptive procedures since deterministic procedures are more efficient in targeting the desired allocation.

Hu and Rosenberger (2003) showed that the power of treatment comparison is closely related to the variability of the allocation proportion: the higher the variability the lower the power. The variability of the allocation proportion depends on the type of allocation procedure as well as on the allocation that the design targets and the amount of randomness it provides. The urn design of Ivanova (2003) yields the lowest variability as it achieves the lower bound of the asymptotic variance of the allocation proportion (Rosenberger and Hu, 2003; Hu, Rosenberger and Zhang, 2006), so does the ERADE (Hu, Zhang and He, 2009). The doubly adaptive coin design achieves the lower bound only when the procedure is deterministic (Rosenberger and Hu, 2003). Randomness and the variability of the allocation proportion in the ERADE and the doubly adaptive coin design depends on the value of the design parameter. When several response adaptive designs that target the same allocation are compared, and their corresponding design parameters are set to provide the same amount of randomness, then the best design is the one that has the lowest variability of the allocation proportion. Zhang et al. (2011) put the lowest variability urn design of Ivanova (2003) and other urn models into a general framework of

immigrated urn models. In this paper, we generalize the design of Ivanova (2003) in a different way by allowing the change in the urn composition to depend on several previous outcomes, not only the most recent outcome. This new generalization allows targeting a large spectrum of allocation proportions, including allocations that yield good power of treatment comparison. Since the design of Ivanova (2003) yields the lowest variability of the allocation proportion the new design has low variability as well and as the result has better power than competitors. The generalization, however, creates challenges in obtaining theoretical properties of the design since the new design can no longer be embedded into a family of stochastic processes unless multidimensional state space is considered.

Our motivating example is the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) trial (Decousus et al., 2010). This was a randomized trial comparing a new drug Arixtra with placebo in patients with acute symptomatic thrombophlebitis of the lower limbs. The primary efficacy outcome was a composite of death from any cause or symptomatic pulmonary embolism or symptomatic deep-vein thrombosis or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis at day 47. The observed success probabilities were 99.1% in Arixtra arm and 94.1% on placebo. Similar success probabilities for placebo are often observed in other cardio-vascular trials. For example, 30-day mortality is a commonly used primary endpoint in trials comparing therapies for acute myocardial infarction, these trials yield around 93% - 95% non-failure rate (Hjalmarson et al., 1985; Tebbe et al., 1998). The incident mortalities are usually compared via log odds ratios. Response adaptive designs are beneficial for trials like these because they reduce the number of failures on average and increase power of treatment comparison, if the treatment is better than placebo, because when highly successful treatments are compared based on log odds

ratios or relative risk the power is maximized when more patients are assigned to the better treatment (Dette, 2004).

In this paper in Section 2 we review possible target allocations for trials comparing two treatments. We introduce higher order urn designs in Section 3. We present the theoretical result for normally distributed outcomes in Section 4. Simulations results are described in Section 5. In Section 6 we re-design the CALISTO trial. Section 7 is a discussion section.

2.2. Optimal allocations

Consider the case where two treatments are compared. Let $N_i(n)$ be the number of subjects assigned to treatment i, i = 1, 2, by the time a total of n subjects have been assigned, $N_1(n) + N_2(n) = n$. The allocation proportion to treatment 1 by the time n patients have been assigned is $N_1(n)/n$. The optimal allocation proportion can be determined by using multiple-objective optimality criteria (see Jennison and Turnbull, 2000, for more details). If treatment outcomes are binary from $Bernoulli(p_i)$, $0 < p_i < 1$, $q_i = 1 - p_i$, i = 1, 2, the allocation proportion on treatment 1, $\rho_1 = \sqrt{p_1 q_1}/(\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$, Neyman allocation, minimizes the variance of $\hat{p}_1 - \hat{p}_2$. Alternatively, it minimizes the total sample size required to achieve given power if the Wald's test statistic is used to test H_0: $p_1 - p_2 = 0$. The allocation that minimizes the expected number of failures for a fixed variance of the estimate of the parameter of interest or for fixed power (Rosenberger et al., 2001) is $\rho_2 = \sqrt{p_1}/(\sqrt{p_1} + \sqrt{p_2})$. Another allocation to mention is $\rho_3 = p_1 q_1/(p_1 q_1 + p_2 q_2)$; it yields the same power as equal allocation (see discussion of ρ_3 in Baldi Antognini and Giovagnoli, 2010). When the log odds ratio, $\log\left[p_1 q_2/(q_1 p_2)\right]$, is estimated

the three corresponding allocations are $\rho_1' = \sqrt{p_2 q_2}\,/(\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$, $\rho_2' = \sqrt{p_2} q_2 \,/\left(\sqrt{p_1} q_1 + \sqrt{p_2} q_2\right)$, and $\rho_3' = p_2 q_2 / (p_1 q_1 + p_2 q_2)$.

Ivanova and Rosenberger (2001) noted that response adaptive designs are most advantageous in trials with highly successful treatments, or equivalently trials with low probability of a bad event occurring for the following two reasons. First, in such trials treatment failure is often death (Hjalmarson et al., 1985; Tebbe et al., 1998) or severe disability (Connor et al., 1994; Simoons et al., 2002; Wallentin et al., 2003) and therefore it is most desirable to minimize the number of treatment failures. Second, if treatments are compared based on log odds ratio, the allocation that maximizes power,, allocation ρ_1', assigns more patients to the better treatment when both success probabilities are higher than 0.5. In the case of highly successful treatments, the allocation ρ_3' might be an even better target for a response adaptive design than the allocation ρ_1' since it assigns even more patients to the better treatment and therefore further reduces the expected number of failures. For example, the optimal allocations for success probabilities $p_1 = 0.991$ and $p_2 = 0.941$ observed in CALISTO trial are $\rho_1' = 0.717$, $\rho_2' = 0.869$ and $\rho_3' = 0.866$. The total number of failures observed in CALISTO trial was 101, 13 out of 1502 in Arixtra arm and 88 out of 1500 in placebo arm. The allocation ratio $\rho_3' = 0.866$ would have yielded 46 total failures out of 3002 patients on average if the true rates were equal to those observed in CALISTO trial, reducing the average number of failures by 55. For small sample sizes the limiting allocation ρ_3' might not be reached, still, the trial most likely will result in an allocation somewhere in $(0.5, \rho_3']$, yielding better power and reduced number of failures

compared to equal allocation. Therefore ρ_3' is an ideal target allocation in trials with highly successful treatments.

2.3. Higher order urn designs for binary outcomes

2.3.1. The second order urn design for binary outcomes

We introduce the second order urn design to create an urn design that focuses on variability of the estimated treatment effect rather than the mean. As a result the new design targets allocation proportions that are optimal or nearly optimal in terms of power, such as allocation ρ_3'. Also, by modifying a low variability design from Ivanova (2003), we obtain another low variability design and therefore we expect the new design to have good power compared to competitors as variability affects power negatively (Hu and Rosenberger 2003).. The design is defined as follows:

Second order urn design. The urn contains balls of three types. Balls of types 1 and 2 represent the two treatments. Balls of type 0 are called immigration balls. Initially the urn contains $2b + a$ balls; b balls of each treatment type and a, $a > 0$, immigration balls. Assume that j patients have been treated so far, with at least one patient assigned to each treatment. If the jth patient was assigned to treatment i, let $X_{N_i(j)}^{(i)}$ be this patient's outcome. A ball is drawn from the urn at random. If the ball is of type 0, i.e., an immigration ball, no subjects are assigned to treatment, and the ball is returned to the urn together with 2 additional balls, one of each treatment type. If a ball corresponding to treatment i is drawn, $i = 1, 2$, the next subject is assigned to treatment i and an outcome $X_{N_i(j)}^{(i)}$ is observed. If $X_{N_i(j)}^{(i)} \neq X_{N_i(j)-1}^{(i)}$, where $X_{N_i(j)-1}^{(i)}$ is

the outcome of the previous subject assigned to treatment i, the ball is not returned. Otherwise, the ball is returned to the urn.

In the urn design of Ivanova (2003) the ball is not returned to the urn if there is a failure on the corresponding treatment. In the second order urn design the ball is not returned to the urn if the two most recent responses on the treatment are different, thus changing the urn composition according to the variability rather than the actual outcome. In this urn design the ball is not returned if outcomes are different, which increases the allocation to the treatment with smaller variance.

2.3.2. Limiting allocation proportion and variability of the second order urn design

When a response adaptive design is investigated, what is most important is the distribution of the proportion of patients assigned to each treatment, specifically the limiting distribution as the number of patients tends to infinity. To obtain this distribution for the second order urn design, we use the technique of embedding the design into a family of continuous time stochastic processes (Ivanova, 2003; Ivanova, 2006). First, we note that the design can be described by using the notion of continuous time (see Ivanova, 2003 and Ivanova, 2006, for more details), which is a useful mathematical construct not related to the real time in the medical experiment. Let $Z_i(t)$ be the number of balls of type i at time t, $U_i(t)$ be the number of draws of a ball of type i followed by a success on treatment i, and $Y_i(t)$ be the number of draws of a ball of type i followed by a failure on treatment i, so that the number of trials on the ith treatment, $i = 1, 2$, is $N_i(t) = U_i(t) + Y_i(t)$. Let $I(t)$, the common immigration process, be the number of draws of balls of type 0, immigration balls. By construction $Z_i(t) = Z_i(0) + I(t) - Y_i(t)$. The number of trials $N_i(t)$ is what interests us most, and the number of balls in the urn, $Z_i(t)$, is the quantity that defines this process. This technique has already been discussed in the stochastic processes literature. Ivanova

et al. (2000) extended the technique from Cox and Miller (1965, p. 265) to obtain the differential equation for the joint probability generating functions. To describe the behavior of $N_i(t)$, we will obtain its joint generating function with the number of balls in the urn, $Z_i(t)$, $G^{(i)}(t,z,w) = E\left(z^{Z_i(t)} w^{N_i(t)}\right)$. Since the two most recent responses are used, consider the generating function $G_0^{(i)}(t,z,w)$ describing the behavior of the process corresponding to treatment *i* when the preceding state was 0, the penultimate on treatment *i* was a success, and the generating function $G_1^{(i)}(t,z,w)$ describing the behavior of the process when the preceding state is 1, the penultimate response on treatment *i* was a failure, with $G^{(i)}(t,z,w) = G_0^{(i)}(t,z,w) + G_1^{(i)}(t,z,w)$. Using backward equations, the following system of equations is obtained (see Appendix I for more details):

$$\begin{aligned} \frac{\partial G_0^{(i)}(t,z,w)}{\partial t} &= \frac{\partial G_0^{(i)}(t,z,w)}{\partial z}(q_i wz - z) + \frac{\partial G_1^{(i)}(t,z,w)}{\partial z} q_i w + a(z-1) G_0^{(i)}(t,z,w) \\ \frac{\partial G_1^{(i)}(t,z,w)}{\partial t} &= \frac{\partial G_1^{(i)}(t,z,w)}{\partial z}(p_i wz - z) + \frac{\partial G_0^{(i)}(t,z,w)}{\partial z} p_i w + a(z-1) G_1^{(i)}(t,z,w) \end{aligned} . \quad (1)$$

Initial and boundary conditions are $G_0^{(i)}(0,z,w) = q_i z$, $G_1^{(i)}(0,z,w) = p_i z$, and $G^{(i)}(t,1,1) = 1$, i = 1, 2, with $t \geq 0$, $|z| \leq 1$, and $|w| \leq 1$.

We are interested in the limiting allocation proportion for the urn $\text{plim}_{n\to\infty}\left\{N_i(n)/n\right\}$, where plim denotes convergence in probability. Ivanova (2003) showed that the limiting proportion can be computed by first obtaining

$$\lim_{t\to\infty} E\left\{N_i(t)\right\} = \lim_{t\to\infty} \left.\frac{\partial\left\{\log G^{(i)}(t,1,w)\right\}}{\partial w}\right|_{w=1} .$$

It might not be possible to obtain the closed form solution of the system of equations (1) except for special cases, however $\lim_{t\to\infty} E(N_i(t)/t)$ can be obtained by taking logs and then differentiating functions in the equations (1). We get $\lim_{t\to\infty} E(N_i(t)/t) = a/(2p_iq_i)$. Using Theorems 3.1 and 3.2 from Ivanova (2000),

$$\text{p}\lim_{n\to\infty}\{N_1(n)/n\} = \frac{a/(2p_1q_1)}{a/(2p_1q_1)+a/(2p_2q_2)} = \frac{p_2q_2}{p_1q_1+p_2q_2},$$

which is ρ_3'.

The variability can be assessed by computing

$$var\{N_i(t)\} = \frac{d}{dw}\left[w\frac{d\{\log G^{(i)}(t,1,w)\}}{dw}\right]\Bigg|_{w=1},$$

$$cov\{N_1(t),N_2(t)\} = \frac{\partial}{\partial w_1}\frac{\partial}{\partial w_2}\log G^{(1,2)}(t,1,w_1,w_2)\Bigg|_{w_1=w_2=1},$$

where $G^{(1,2)}(t,1,w_1,w_2)$ is a joint function for $N_1(t)$ and $N_2(t)$ (see Ivanova, 2006, for details). It was not possible to obtain the closed form expressions for $var\{N_1(t)\}$, $var\{N_2(t)\}$ and $cov\{N_1(t),N_2(t)\}$ for given t and as $t\to\infty$ so we resorted to numerical computations.

2.3.3. Higher order urn designs for binary outcomes

In Section 3.1 we introduced the design that is an extension of the low variability design from Ivanova (2003) and uses two most recent responses instead of one response as in the original Ivanova design. In this section we extend the design further by using three or more responses. This extension creates designs that target an even wider range of allocation proportions and converge faster than the second order urn design while keeping variability low as before.

To describe this extension we first note that the second order design defined in Section 3.1 can be alternatively defined using the estimate of success probability obtained from the two most recent observations. The estimate $\hat{p}_i = \left(X^{(i)}_{N_i(j)} + X^{(i)}_{N_i(j)-1} \right)/2$, i =1, 2, can take on three possible values 0, 1/2 and 1. The ball of type i is not returned if $\hat{p}_i = 0.5$. Similarly, in the kth order urn design, the estimate of success rate is based on the k most recent responses: $\hat{p}_i = \sum_{m=1}^{k} X^{(i)}_{N_i(j)-m+1}/k$. Let an integer α be such that $k = 2\alpha$, if k is even, or $k = 2\alpha+1$, if k is odd. Consider the *kth* order design where the ball is not returned if $\hat{p}_i = \alpha/k$ or $\hat{p}_i = 1-\alpha/k$, that is, the ball is not returned if the estimate of success rate is the closest possible to 0.5. The probability of not returning the ball is $Q_i = C^k_\alpha p_i^\alpha q_i^\alpha$ if $k = 2\alpha$, or $Q_i = C^k_\alpha p_i^{\alpha+1} q_i^\alpha + C^k_\alpha p_i^\alpha q_i^{\alpha+1} = C^k_\alpha p_i^\alpha q_i^\alpha (p_i + q_i) = C^k_\alpha p_i^\alpha q_i^\alpha$ if $k = 2\alpha+1$. Here $C^k_\alpha = k!/\left[\alpha!(k-\alpha)!\right]$ is a binomial coefficient with $C^k_\alpha = 0$, if $\alpha < 0$ or $\alpha > k$. The limiting allocation proportion for this urn design (Ivanova, 2003) is equal to $Q_2/(Q_1+Q_2) = p_2^\alpha q_2^\alpha/(p_1^\alpha q_1^\alpha + p_2^\alpha q_2^\alpha) = \rho(\alpha)$. For example, when k = 3 the limiting allocation proportion is $\rho(1) = p_2 q_2/(p_1 q_1 + p_2 q_2) = \rho'_3$, when k = 4, the allocation is $\rho(2) = p_2^2 q_2^2/(p_1^2 q_1^2 + p_2^2 q_2^2)$. For $p_1 > p_2$ and $\alpha > \beta$, $\rho(\alpha) > \rho(\beta)$, therefore for all $\alpha > 1$ $\rho(\alpha)$ is closer to 1 than $\rho(1) = \rho'_3$. Allocations $\rho(\alpha)$ for $\alpha > 1$ might be desirable for trials with the goal of selecting the best treatment, however, as was discussed in Section 2, the power under allocations $\rho(\alpha)$ with $\alpha > 1$ is lower than under ρ'_3 or under equal allocation.

With the use of a biased coin the kth order urn design can be made to target the desirable allocation ρ'_3. Consider a kth order urn design, k = 4, 5…, where the ball is not returned if $\hat{p}_i = m/k$ or $\hat{p}_i = 1-m/k$, m = 1,…, k -1, and a biased coin with probability of heads equal to

$C_\alpha^k C_{m-1}^{k-2} / \left(C_{\alpha-1}^{k-2} C_m^k \right)$ lands heads. To compute the limiting allocation proportion for this design we first compute the probability of not returning the ball

$$Q_i = \sum_{m=1}^{k-1} \frac{C_\alpha^k}{C_{\alpha-1}^{k-2}} \frac{C_{m-1}^{k-2}}{C_m^k} C_m^k p_i^m q_i^{k-m} = \frac{C_\alpha^k}{C_{\alpha-1}^{k-2}} p_i q_i \sum_{m=1}^{k-1} C_{m-1}^{k-2} p_i^{m-1} q_i^{k-m-1}$$
$$= \frac{C_\alpha^k}{C_{\alpha-1}^{k-2}} p_i q_i \sum_{m'=0}^{k-2} C_{m'}^{k-2} p_i^{m'} q_i^{k-2-m'} = \frac{C_\alpha^k}{C_{\alpha-1}^{k-2}} p_i q_i (p_i + q_i)^{k-2} = \frac{C_\alpha^k}{C_{\alpha-1}^{k-2}} p_i q_i .$$

Therefore the limiting allocation is equal to $Q_2 /(Q_1 + Q_2) = p_2 q_2 /(p_1 q_1 + p_2 q_2) = \rho_3'$. For example, when k = 4, the possible values for $\hat{p}_i$ are 0, 1/4, 1/2, 3/4, and 1. According to the design described above, the ball is not returned if $\hat{p}_i = 1/2$; or if $\hat{p}_i = 1/4, 3/4$ and a biased coin with the probability of heads equal to 3/4 lands heads. When k = 5, the ball is not returned if $\hat{p}_i = 2/5, 3/5$; or if $\hat{p}_i = 1/5, 4/5$ and a biased coin with the probability of heads equal to 2/3 lands heads.

2.4. Higher order urn designs for normally distributed outcomes

In this section we define the kth order urn design for continuous outcomes and prove a result about its limiting allocation. As response adaptive designs are mostly advantageous when treatments with binary outcomes are compared (unless the variances of continuous responses in the two arms are very different), the goal of this section is to provide insights into how to construct higher order urn designs for binary outcomes that yield good power of treatment comparison.

Let responses to the two treatments coming from $N(\mu_i, \sigma_i^2)$, and $\hat{\mu}_i$ be the maximum likelihood estimate of μ_i, i = 1, 2. The allocation proportion that minimizes the variance of

$\hat{\mu}_1 - \hat{\mu}_2$ is the Neyman allocation $\rho_{Ney} = \sigma_1/(\sigma_1 + \sigma_2)$. Assume that outcomes of treatment *i* come from $N(\mu_i, \sigma_i^2)$ and let $\hat{\sigma}_i^2$ be the estimate of the variance based on the *k* most recent observations on treatment *i*, defined as

$$\hat{\sigma}_i^2 = \sum_{m=1}^{k} \left(X_{N_i(j)-m+1}^{(i)} - \bar{X} \right)^2 / (k-1), \text{ where } \bar{X} = \sum_{m=1}^{k} X_{N_i(j)-m+1}^{(i)} / k.$$

Then, the ball is not returned to the urn if $\hat{\sigma}_i^2 < \delta$ for some δ. The following theorem characterizes the limiting distribution.

Theorem. As $\delta \to 0$, the limiting allocation proportion for the *k*th order urn design, $k > 1$, with normally distributed outcomes tends to $\rho = \sigma_1/(\sigma_1 + \sigma_2)$.

Proof. The distribution of $(k-1)\hat{\sigma}_i^2/\sigma_i^2$ is chi-squared with degrees of freedom $df = k-1$. Let *F* be the cumulative distribution function of chi-squared distribution with $df = k-1$, and *f* be its density function. The probability of not returning the ball is $F\left((k-1)\delta/\sigma_i^2\right)$ and the limiting proportion is (Ivanova, 2003)

$$\operatorname*{plim}_{n\to\infty} \frac{N_1(n)}{n} = \lim_{\delta\to 0} \frac{F\left((k-1)\delta/\sigma_1^2\right)}{F\left((k-1)\delta/\sigma_1^2\right) + F\left((k-1)\delta/\sigma_2^2\right)}.$$

Now it follows from L'Hôpital's Rule that:

$$\lim_{\delta\to 0} \frac{F\left((k-1)\delta/\sigma_1^2\right)}{F\left((k-1)\delta/\sigma_1^2\right) + F\left((k-1)\delta/\sigma_2^2\right)} = \lim_{\delta\to 0} \frac{f(\delta/\sigma_1^2)/\sigma_1^2}{f(\delta/\sigma_1^2)/\sigma_1^2 + f(\delta/\sigma_2^2)/\sigma_2^2} = \frac{\sigma_2}{\sigma_1 + \sigma_2},$$

since $f(x) \propto x^{k/2-1} e^{-x/2}$.

Hence, if a sufficiently small δ is chosen, the limiting allocation for the *k*th order urn design with normal outcomes and any *k* >1 will be close to Neyman allocation. This result gives

basis to the general strategy of constructing higher order urn designs for binary outcomes described in previous sections.

2.5. Comparison with competing designs

In this section we compare the new urn designs with the doubly adaptive biased coin design (Hu and Zhang, 2004) and the efficient randomized adaptive design (Hu, Zhang and He, 2009).

The doubly adaptive biased coin design (Hu and Zhang 2004) allocates patient j to treatment i with probability $g(N_i(j)/(j-1), \hat{\rho})$, where $\hat{\rho}$ is the target proportion estimated from the data. We use the choice of g from Hu and Zhang (2004):

$$g(x,\rho) = \frac{\rho(\rho/x)^{\gamma}}{\rho(\rho/x)^{\gamma} + (1-\rho)\left[(1-\rho)/(1-x)\right]^{\gamma}},$$
$$g(0,\rho) = 1,$$
$$g(1,\rho) = 0.$$

Here γ is a design parameter controlling the amount of randomization in the design. Let $\rho(p_1, p_2)$ be the target allocation proportion as a function of p_1 and p_2, for example, $\rho(p_1, p_2) = \sqrt{p_2 q_2}\,/\left(\sqrt{p_1 q_1} + \sqrt{p_2 q_2}\right)$ for inverse Neyman allocation. Hu and Zhang (2004) give the following formula for the asymptotic variance, ω^2, of $N_1(n)/n$

$$\omega^2 = \frac{\omega_1^2}{1+2\gamma} + \frac{2(1+\gamma)}{1+2\gamma}\omega_2^2, \text{ where}$$
$$\omega_1^2 = \rho(p_1, p_2)\left[1-\rho(p_1, p_2)\right] \text{ and}$$
$$\omega_2^2 = \left(\frac{\partial\rho(p_1, p_2)}{\partial p_1}\right)^2 \frac{p_1 q_1}{\rho(p_1, p_2)} + \left(\frac{\partial\rho(p_1, p_2)}{\partial p_2}\right)^2 \frac{p_2 q_2}{1-\rho(p_1, p_2)}.$$

When $\gamma = 0$, the design is fully randomized, and the variance is $\omega_1^2 + 2\omega_2^2$; when $\gamma = +\infty$ the design is deterministic, the variance is ω_2^2 and is equal to the lower bound of the asymptotic variance. Hu and Rosenberger (2005) recommended using the design with $\gamma = 2$.

The ERADE (Hu, Zhang and He, 2009) is a generalization of Efron's coin which attains the lower bound of the asymptotic variance and can target any desirable allocation. The ERADE requires specifying a design parameter π, $0 \le \pi < 1$, that reflects the degree of randomization, with larger values of π corresponding to more randomization and variability. The design is defined as follows. As before, $\hat{\rho}$ is the estimated target allocation for treatment 1. Then the next patient is assigned to treatment 1 with probability $\hat{\rho}\pi$ if the actual allocation to treatment 1 exceeds $\hat{\rho}$; with probability $\hat{\rho}$ if the two estimated allocations are equal; with probability $1-(1-\hat{\rho})\pi$ if the actual allocation exceeds the estimated target allocation. Hu, Zhang and He (2009) studied the choice π and found that the simulated results of π = 1/8 and 1/4 were very similar to the results of π = 1/2 in terms of allocation proportion and its variability, and the ERADE with π = 3/4 has a slightly larger variability than others. They recommended using π in [0.4, 0.7]. Since the ERADE with π = 0.5 performed very similar to lower values of ERADE we used the ERADE with π = 0.5.

We compared designs based on variability of allocation proportion and randomness. Randomness was quantified by summing entropy of the allocation distribution for each assignment, $-\sum_{j=1}^{N} \xi_j \log(\xi_j)$, where ξ_j is the probability of being assigned to treatment 1 after (j – 1) patients have been assigned. For a given p_1 and p_2, the sample size, N, used for entropy calculations was that which yields 80% power with a two-sided type I error rate of 0.05 for

testing based on the log odds ratio. For the adaptively biased coin design $\xi_j = g(N_1(j)/(j-1), \hat{\rho})$. In the case of the third order urn design, ξ_j is equal to $\sum_{m=0}^{\infty}(z_1(j)+m)\left\{\prod_{k=0}^{m}(z_1(j)+z_2(j)+1+2k)\right\}^{-1}$, where $z_i(j)$ is the number of balls of type *j* in the urn right after the most recent treatment (non-immigration) ball was chosen, and the sum is over the number of immigration balls *m* to be drawn before a treatment ball is drawn. The product in the denominator is the probability that *m* - 1 immigration balls are chosen before $z_i(j)$ is finally chosen. We have not been able to obtain a closed form for the sum. Noting that that the sum of all terms after the *m*th term is less than the *m*th term (see Appendix II) it is easy to obtain the numerical value for the sum with any degree of accuracy. We computed the sum within 10^{-14} of the true value.

First, we compare the asymptotic variance of the second and third order urn designs with the lower bound of the asymptotic variance of designs that target ρ_3' and the asymptotic variance of the doubly adaptive biased coin design with $\gamma = 2$. Fig. 1 displays the asymptotic variances for $p_2 = 0.90$ and p_1 in [0.90, 0.99]. Even though the design from Ivanova (2003) achieves the lower bound of the asymptotic variance, the higher order urn designs do not, but their variances are very close to the lower bound and are significantly smaller than those of the biased coin design with $\gamma = 2$.

Second, we compared the designs for sample sizes required to achieve 80% power for treatment comparison if equal allocation was used. We compared the second and third order urn designs to the adaptively biased coin design with $\gamma = 2$ and ERADE with $\pi = 0.5$ for values of p_1 and p_2 greater than 0.5 based on the variance of the allocation proportion and on the amount of

randomness the designs provide. The regions of (p_1, p_2) sample space where the third order urn design has higher entropy, which is more desirable, are marked with vertical lines in Fig. 2. Elements of (p_1,p_2) space where the asymptotic variance for the third order urn design was smaller marked with horizontal lines in Fig. 2. In Section 2 we proposed ρ_3' as the target allocation in a trial where treatment comparison is based on log odds ratio. The first row of Fig. 2 shows the comparison with the adaptively biased coin design and the ERADE targeting ρ_3', the second row targeting ρ_1'. Fig. 2 shows that the third order urn design performs well against the adaptively biased coin design and the ERADE targeting ρ_3' in about half of the 2-dimensional region of (p_1, p_2). When the coin design and the ERADE target ρ_1' the region where the new design is better is smaller, however, the advantage of the proposed design still holds for trials where highly successful treatments are compared.

2.6. Example: re-designing CALISTO trial

The proposed approach is illustrated by re-designing the CALISTO trial (Decousus et al., 2010). The total sample size in the trial was 3002 patients with 1502 patients assigned to Arixtra and 1500 to placebo. The sample size of 3000 was chosen because it yields the power of 87% to detect a 2 percentage point absolute increase in incidence of events at the two-sided 0.05 level of significance using Fisher's exact test, provided the incidence in the placebo group is no greater than 2%. Observed success probabilities were $p_1 = 0.991$ in the Arixtra arm and $p_2 = 0.941$ in placebo arm. Corresponding optimal allocations are $\rho_1' = 0.717$, which minimizes the sample size given power, and $\rho_2' = 0.869$, which minimizes the expected number of failures given

power. Our proposed urn design targets $\rho_3' = 0.866$, the allocation that yields the same power as equal allocation by less treatment failures. For the success probabilities in CALISTO trial both the coin design and the ERADE perform better when targeting ρ_1', therefore we describe simulation results for these two designs for ρ_1' target only. To redesign the CALISTO trial we first found the values of parameters γ in the coin design and π in the ERADE design that yield the same randomness, measured by the total entropy, as the third order urn design. These parameters were $\gamma = 0$ for the coin design and π = 0.28 for the ERADE. Then trials with assignments by the coin design and the ERADE were simulated. Results are presented based on 5000 simulated trials. Simulation study was repeated with recommended values $\gamma = 2$ and π = 0.5 yielding similar conclusions. To simulate CALISTO trial we resampled from CALISTO data knowing that 13 out of 1502 failures were observed in Arixtra arm and 88 out of 1500 in placebo arm. Results when data were simulated from Bernoulli distribution with success probabilities $p_1 = 0.991$ and $p_2 = 0.941$ were very similar. If equal allocation is used and true probabilities are $p_1 = 0.991$ and $p_2 = 0.941$, 536 subjects total are required to achieve 90% power with two-sided test with the type I error rate of 0.05. As the sample size in CALISTO trial was much larger than needed we re-designed the trial as a two-stage trial with 1500 patients in each stage with the Pocock boundary (Pocock, 1977) to allow stopping early for efficacy. In fact, all trials were stopped for efficacy after 1500 patients. The average number of failures and the 5th and 95th percentiles were 33 (25, 42) for the coin design, 34 (28, 41) for ERADE, 30 (26, 34) for the urn design and 50 (43, 59) for equal allocation. All response adaptive designs dramatically reduced the total expected failures with the new urn design yielding the smallest number of failures.

Fig. 3 shows power curves in the informative region of total sample sizes, between 300 and 600, for the third order urn design, the ERADE, and equal allocation. Power for the adaptively biased coin design is inferior and is not shown. As seen from Fig. 3, the proposed urn design has better power than equal allocation and the ERADE. Better power for the urn design is the result of low variability of the allocation proportion (Fig. 4). The average allocation proportion and its 25th and 75th percentiles (Fig. 4) show that the allocation proportion of the doubly adaptive coin design and the ERADE converges to the limiting proportion quickly, but that the variability of the allocation proportion is high. For example, for the total sample size of 300, the allocation proportion in 10% of the trials is 90:10 or more extreme when the target is, in fact, $\rho_1' = 0.717$. This makes the design more sensitive to time trends and lower in power when multiple interim analyses are performed. Though the urn design converges slower, it is far less variable.

We also performed simulations with delayed response. As shown by Bai, Hu and Rosenberger (2002) the asymptotic properties of response adaptive designs under delay in outcome are the same as without a delay unless the delay is substantial and as long as adaptations are done frequently. We assumed that the data from the first patient was only available when the kth patient was enrolled, the data from the second patient was available when the (k+1) patient was enrolled etc. For example, if $k \geq 1500$ in a trial with 1500 patients total, no data are available to modify the allocation proportion. A delay with k = 500 yielded 39, 39 and 38 failures on average for the coin design, the ERADE and the urn design with fewer failures observed on average than 50 failures under equal allocation. Significant delay of k = 1000 in a trial of 1500 yielded 44, 44 and 45 failures on average for the three adaptive designs, only slightly fewer failures than under equal allocation with faster converging coin and ERADE designs now

performing better than the urn design. Note that if the adaptations of the allocation proportion are only performed once or twice during the trial, the proposed urn design is not suitable and the adaptively biased coin or the ERADE should be used. Both the coin design and the ERADE estimate the success probabilities using all available data and compute the desirable allocation proportion.

2.7. Conclusions

The doubly adaptively biased coin design and ERADE estimate the target allocation from the data and therefore can target any desired allocation proportion. Both designs converge rapidly to the target, however, the variability of the allocation proportion is high as well. The proposed higher order urn designs converge to the target allocation more slowly, however, are far less variable. In the example considered, the third order urn design does not result in extreme allocations and yields higher power than the doubly adaptive coin design, the ERADE and equal allocation. Another advantage of the proposed urn designs is that one does not have to know the most recent estimates of the treatments' success probabilities p_1 and p_2. For the third order urn design, for example, one only needs to know if there were any failures among the most recent 3 responses. Therefore, if data used for a recent adaptation are revealed, an investigator will not know the most recent estimates of p_1 and p_2.

In the CALISTO trial example where two highly successful treatments were compared, all three response adaptive designs yielded substantial savings in failures compared to equal allocation. The proposed third order urn design and the ERADE resulted in similar or better power than equal allocation. Therefore, it is worth considering response adaptive designs as a design option for trials with highly successful treatments.

Figure 2.1. The asymptotic variance. Consider the second order urn design (dashed line), the third order urn design (dotted line) and the doubly adaptive biased coin design with parameters $\gamma = 2$ (upper solid line) and $\gamma = \infty$ (lower solid line). Success rate $p_2 = 0.9$.

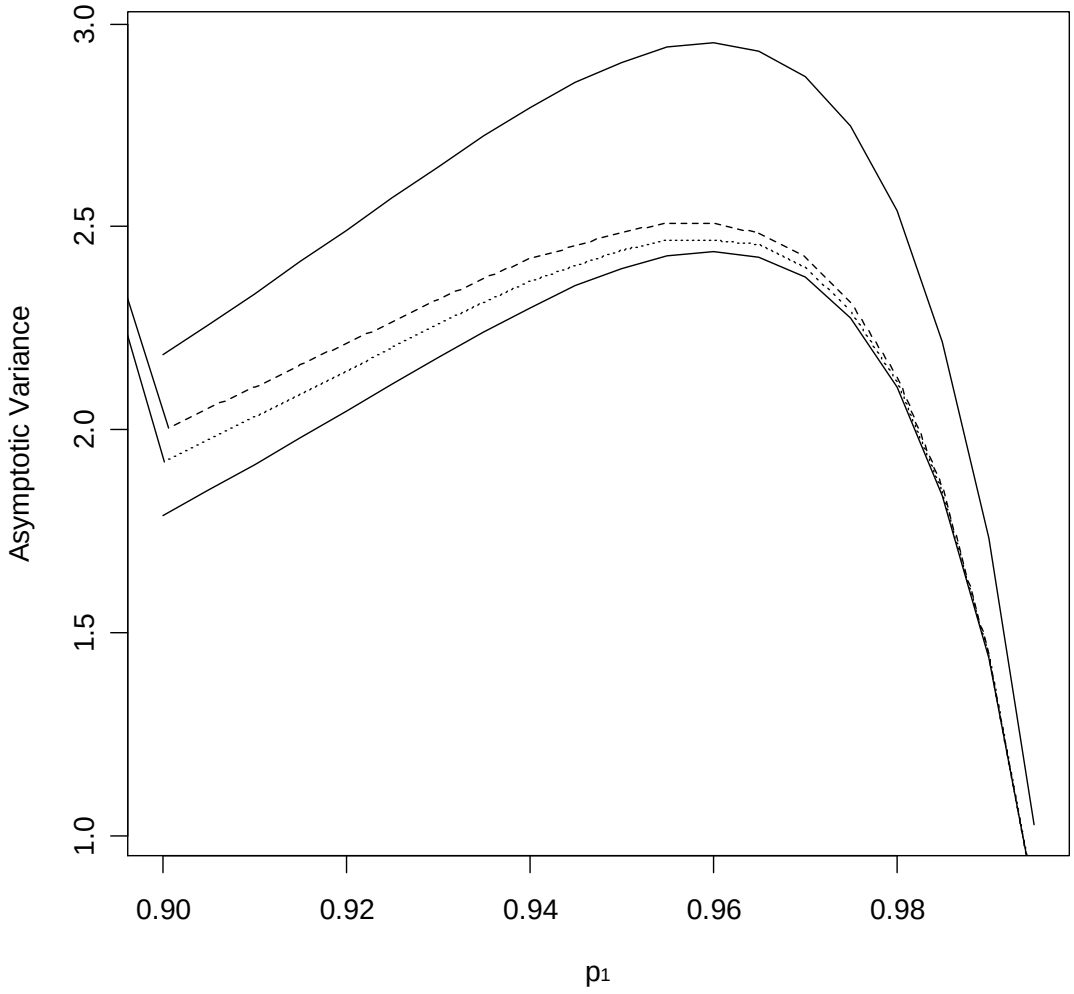


Figure 2.2. Range of success probabilities p_1 and p_2. When third order urn design has smaller asymptotic variance (horizontal lines) and higher entropy (vertical lines) than the doubly adaptive coin design with $\gamma = 2$ (left panel) or ERADE with $\pi = 0.5$ (right panel). The diagonal line is the boundary of the sample space. The first row is for the coin design and ERADE targeting ρ_3', the second for ρ_1'.

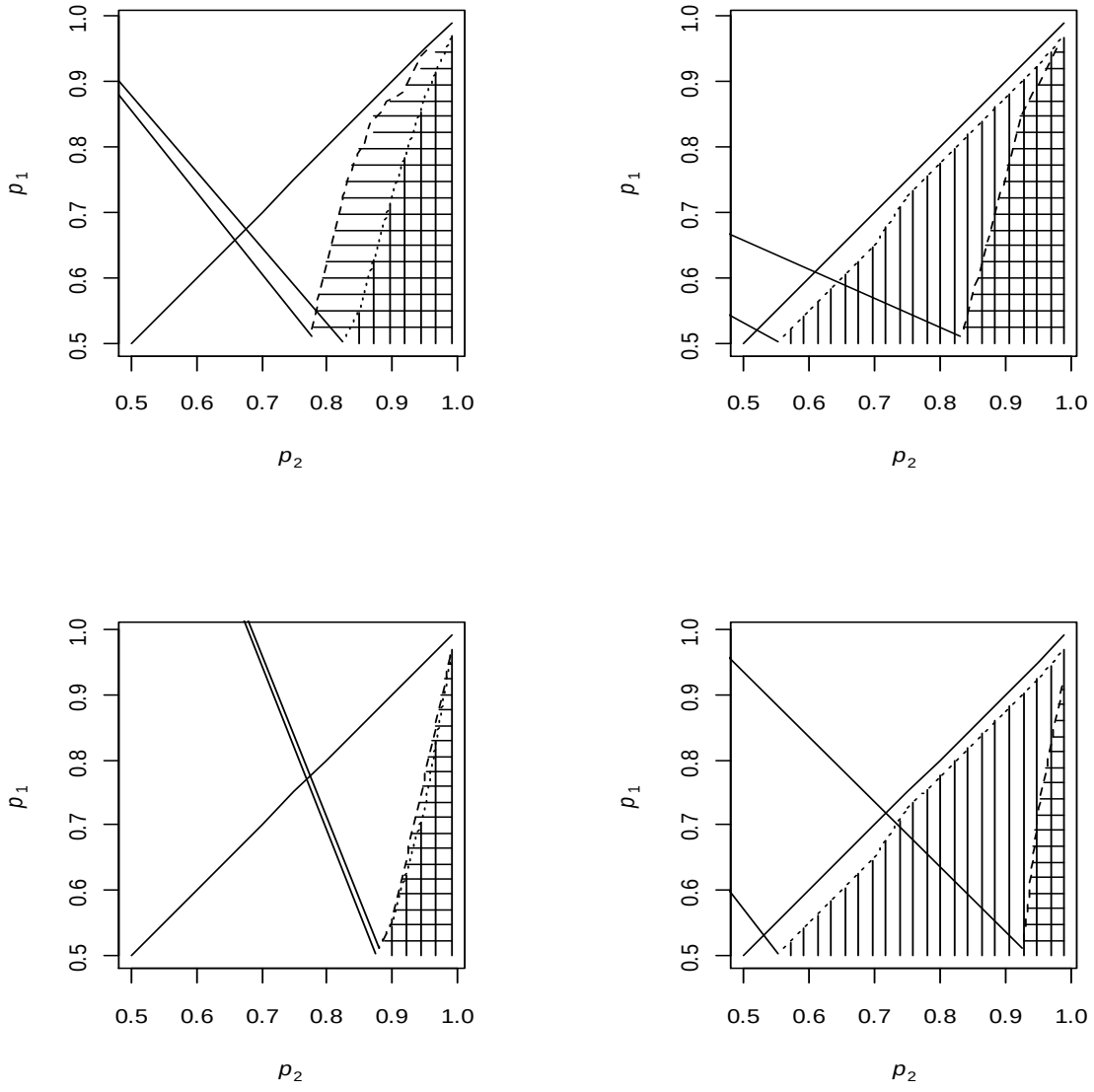


Figure 2.3. Power for the CALISTO trial. Consider $p_1 = 0.991$ and $p_2 = 0.941$ for third order urn design (solid line), the equal allocation (dotted-dashed line) and the ERADE with $\pi = 0.28$ targeting ρ_1' (dotted line).

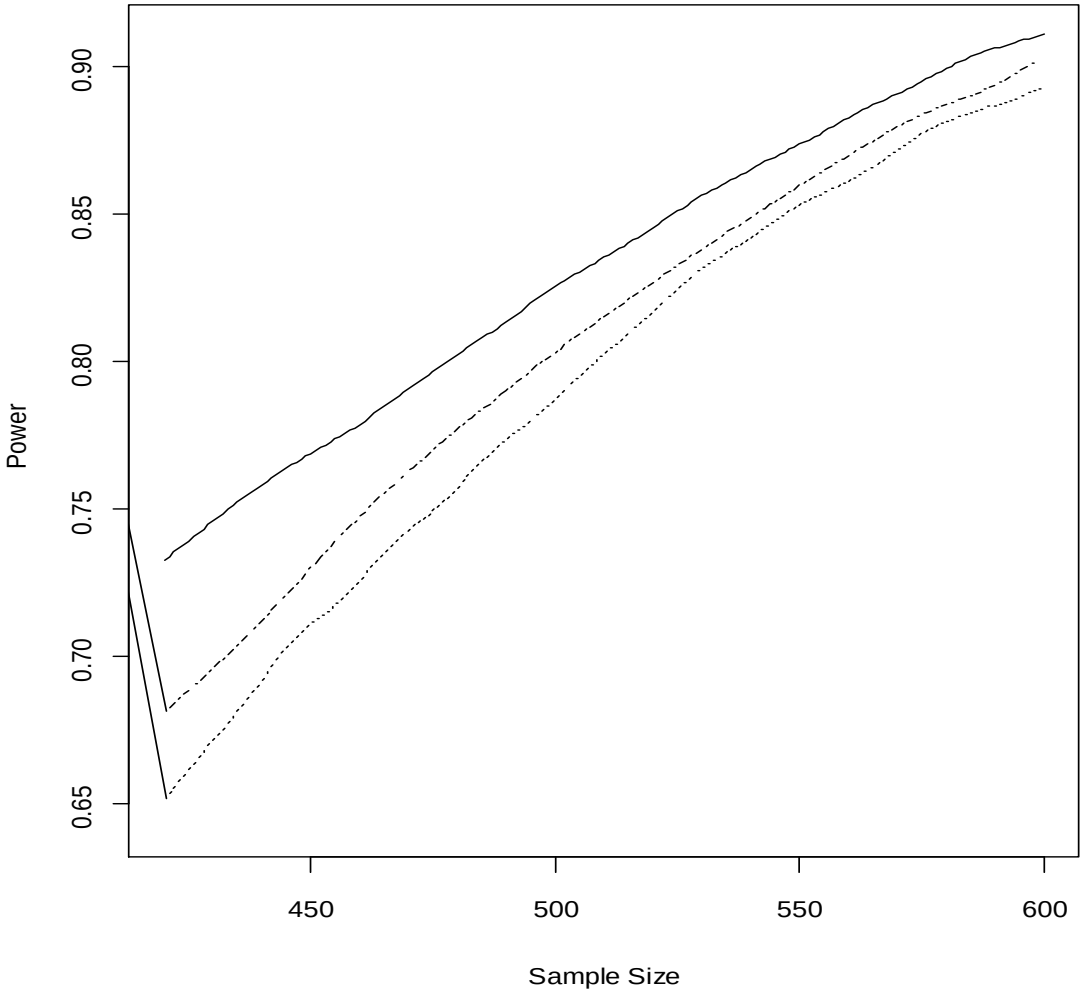
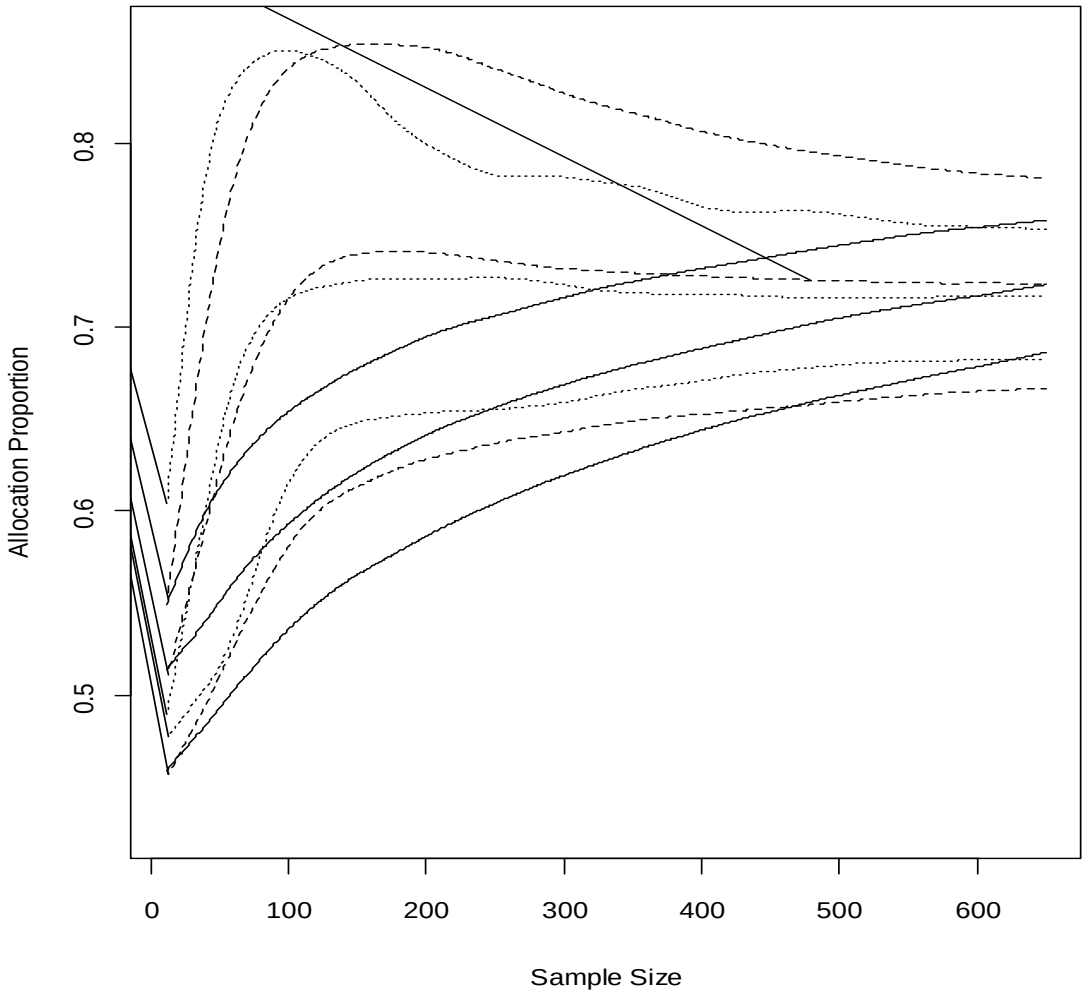


Figure 2.4. Allocation proportion and quantiles. The allocation proportion and its 25th and 75th percentiles for the trial with $p_1 = 0.991$ and $p_2 = 0.941$ for third order urn design (solid lines), the doubly adaptive coin design with $\gamma = 2$ (dashed lines), and ERADE with $\pi = 0.5$ (dotted lines) plotted against the sample size.



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CHAPTER 3: THE PROPERTIES OF ENTROPY AS A MEASURE OF RANDOMNESS IN THE CLINICAL TRIAL

3.1. Introduction

The interpretation of between-group comparisons in a clinical trial is facilitated by the creation of treatment groups that are similar to each other in baseline composition. Selection bias is a major impediment to baseline similarity of treatment groups especially in unmasked clinical trials. Selection bias occurs when expected responders are enrolled or denied enrollment based on the knowledge of treatment to be allocated next (Blackwell and Hodges, 1957), and how healthy the patients are. To minimize selection bias one needs to minimize predictability of future allocations based on past ones. One way to measure predictability is to define a reasonable guessing strategy and then compute the expected number of correctly predicted treatment assignments. Allocation procedures that minimize selection bias against various guessing strategies have been identified (Blackwell and Hodges, 1975; Stigler, 1969). One drawback to this approach is that it is somewhat arbitrary, because the expected value is just one measure of a distribution. Also, this requires assumptions about the distribution of healthiness in the patient population, which is generally difficult to evaluate. Finally, in a clinical trial where a response adaptive randomization design is used, it is not clear what the best guessing strategy for the investigator is, and thus it is not clear how to calculate bias.

A canonical way to measure predictability is to quantify the amount of information the investigator has about the next treatment assignment, given that certain previous treatment

assignments are known. This approach relies on information theory, specifically, Claude Shannon's definition of entropy (Shannon 1959), which quantifies the amount of information observer has about the values a random variable may take. The greater the entropy, the less information the observer has. The formula for entropy of a discrete probability distribution taking on *k* values (which is the type of distribution the treatment assignment random variable will have) is

$$\sum_{i=1}^{k} -p_i \log(p_i),$$

where there are *k* different possible treatments, and p_i is the probability of the *ith* treatment being assigned given some prior knowledge about the trial. Entropy can range from zero, when the next treatment assignment is certain, to log(*k*), when each of the *k* treatments are equally likely. This maximum value is well known and can be found using Lagrange multipliers. This definition of information is very well established in the statistical literature because it has certain desirable properties, which we will not discuss here. Clearly we want the entropy of an allocation scheme to be large, because that would mean that the next treatment assignment is less predictable. Entropy has appeared in the clinical trials literature before, but has not been used to quantify the overall randomness of the trial. The first application was minimizing imbalance in a trial where there were several stratification factors (Klotz, 1978). The author proposed assigning the next treatment so as to minimize the entropy of each treatment assignment with respect to a constraint that is a function of the imbalance. However, the average entropy over the whole trial and how to maximize it was not discussed. Ball et al. (1993) measured treatment assignment uncertainty by entropy and used entropy as a penalty in an objective function that combined the precision of estimation of parameters of interest in a clinical trial. In the objective function, the entropy was

multiplied by a penalty factor that was essentially arbitrary. In contrast, our approach to entropy first optimizes the power and then optimizes the entropy subject to that constraint, and there are no arbitrary parameters. Atkinson (2002) used the idea of Ball et al. (1993) to create allocation design that balances randomness and inference. A more recent paper (Piantadosi, 2005) used entropy as a way of quantifying uncertainty about the treatment effect in a small trial, but it did not explore the concept of using entropy to quantify prior knowledge about upcoming treatments as related to bias. This paper also did not consider trials of arbitrary size.

In Section 2 we develop notation and define the important concepts. In Section 3 we state the main results of our paper. In Section 4 we consider several randomization designs and response adaptive randomization designs to illustrate theoretical results from Section 3. Section 5 is the discussion section.

3.2. Notation

Consider a clinical trial with treatments "A" and "B" where the outcome is measured as either success or failure. Let the binary sequence $\boldsymbol{X}^{(n)} = X_1, X_2, \ldots, X_n$ denote the sequence of treatment assignments for a trial of length *n*. One example could be $\boldsymbol{X}^{(4)} = A, B, A, B$. We assume that all previous treatment assignments may be known. Let the binary sequence $\boldsymbol{Y}^{(n)} = Y_1, Y_2, \ldots, Y_n$ denote the sequence of outcomes, where "0" represents a failure and "1" represents a success, e.g. $\boldsymbol{Y}^{(4)} = 0,1,1,0$. We assume further that for any *j*, *j* = 1,.., *n*, $\Pr\left(Y_j = 1 | X_j = A\right) = p_A$ and $\Pr\left(Y_j = 1 | X_j = B\right) = p_B$. The goal of the trial is to gain information about unknown p_A and p_B. By the trial data of length *n*, $\boldsymbol{D}^{(n)}$ we simply mean

$\boldsymbol{D}^{(n)} = \{\boldsymbol{X}^{(n)}, \boldsymbol{Y}^{(n)}\}$. For a given trial of length n let $N_{n,A}$ denote the number of treatment assignments to A. We define the allocation proportion as $N_{n,A}/n$. If $\Pr\left[X_n = A | \boldsymbol{D}^{(n-1)}, f()\right] = f(\boldsymbol{D}^{(n-1)})$ then we say $f()$ is a treatment allocation function for the trial. By a trial of length n, $\boldsymbol{T}^{(n)}$, we mean $\boldsymbol{T}^{(n)} = \{\boldsymbol{D}^{(n)}, p_A, p_B, f()\}$. Here $\boldsymbol{D}^{(n)}$ is the random part of the trial. Each $\boldsymbol{T}^{(n)}$ has a well defined probability $\Pr(\boldsymbol{T}^{(n)}) = \Pr(\boldsymbol{D}^{(n)} \mid p_A, p_B, f())$. Note that $\Pr(X_n = A | \boldsymbol{D}^{(n-1)}, f())$ is a random variable that depends only $\boldsymbol{D}^{(n-1)}$ and $f()$, while $\Pr(X_n = A)$ is fixed number that is a function of p_A, p_B and $f()$. Let the trial set $\boldsymbol{S}^{(n)}$ be defined as:

$$\boldsymbol{S}^{(n)} = \left\{ \text{all possible } \boldsymbol{T}^{(n)} \right\} \text{for a fixed triple } (p_A, p_B, f()).$$

Note $\sum_{\boldsymbol{T}^{(n)} \in \boldsymbol{S}^{(n)}} \Pr\left(\boldsymbol{T}^{(n)}\right) \equiv 1$ and $\left|S^{(n)}\right| = 2^{2n}$.

Let the trial sequence $\boldsymbol{C}$ be defined as the collection of $\{\boldsymbol{S}^{(1)}, \boldsymbol{S}^{(2)}, \ldots\}$; it is countably infinite. We say the trial sequence targets allocation proportion ρ if for any $\varepsilon > 0$ and $\delta > 0$ there is an $m \in N$ such that $n > m$ implies

$$\sum_{\boldsymbol{T}^{(n)} \in \boldsymbol{S}^{(n)}} I\left[\frac{N_{n,A}}{n} \in (\rho - \varepsilon, \rho + \varepsilon)\right] \Pr\left(\boldsymbol{T}^{(n)}\right) > 1 - \delta .$$

where $I()$ is an indicator function. Not all clinical trial sequences target an allocation.

When $\boldsymbol{C}$ targets an allocation ρ we define the asymptotic variance as $\lim_{n \to \infty} Var\left[\sqrt{n}(N_{n,A}/n - \rho)\right]$, where the variance is taken over all possible trials in $\boldsymbol{S}^{(n)}$. This limit may be zero and also it may not exist. This definition of asymptotic variance coincides with that used in the literature (Hu and Zhang, 2004).

We consider the random variable

$$P_n = \Pr\left(X_n = A | \boldsymbol{D}^{(n-1)}, f() \right).$$

Since the number of trials of length *n* is always finite, P_n is a discrete random variable with support on [0, 1]. Its density can be computed as follows

$$f_{P_n}(p) = \sum_{T^{(n-1)} \in S^{(n-1)}} I\left[\Pr\left(X_n = A \,|\, D^{(n-1)}, f() \right) = p \right] \Pr(T^{(n-1)}),$$

Note that this is distinct from:

$$\sum_{\boldsymbol{T}^{(n-1)} \in \boldsymbol{S}^{(n-1)}} \Pr\left[X_n = A | \boldsymbol{D}^{(n-1)}, f() \right] \Pr\left(\boldsymbol{T}^{(n-1)} \right) = \Pr(X_n = A).$$

This second quantity is just the unconditional probability that the *nth* patient receives treatment *A*, which is not random. The density of P_n, $f_{P_n}(p)$, is the marginal distribution of the conditional probabilities. We now present several examples of P_n. Histograms for the three examples are presented in Figure 2.1.

Example 1, biased coin: Consider a clinical trial allocation scheme that consists of assigning patient *n* to a treatment by flipping a coin that has probability ρ of coming up heads. If the coin comes up heads, the patient receives treatment *A*; if the coin comes up tails, the patient receives treatment *B*. While the allocation proportion to treatment *A* may vary during the trial, P_n is the same for each patient – just a point mass at ρ. Figure 2.1 shows the density function for $\rho = 0.5$, the fair coin design.

Example 2, two-sequence assignment: A fair coin is flipped. If it lands heads, then the trial proceeds as *A*,*B*,*A*,*B*,*A*,*B*… If it lands tails, then the trial proceeds as *B*,*A*,*B*,*A*,*B*,*A*… In this case, the random variable P_n takes on the values 0 and 1. For each patient, P_n is 0 with

probability 0.5, and 1 with probability 0.5. This is because there are exactly two equally likely trials of length *n*, and the allocation probability for the *nth* patient is completely determined by that of the first *n*-1 patients, so the probability conditional on the assignments of the first *n*-1 is either 0 or 1. However, the (unconditional) probability that the *nth* patient is assigned treatment *A* is simply 0.5. Thus, this example illustrates the difference between this probability and P_n.

Example 3, adaptive biased coin: Consider this allocation function, which targets the allocation proportion 0.5:

$$\Pr\left(X_n = A|\boldsymbol{D}^{(n-1)}, f()\right) = f\left(\boldsymbol{D}^{(n-1)}\right) = 1 - N_{(n-1),A}/(n-1)$$

$$= 1 - \text{current allocation proportion.}$$

Note that for a clinical trial set with this allocation function, Pr($\boldsymbol{X}^{(n)}$) does not depend on p_A and p_B. For this design, we see that the allocation proportion $N_{n,A}/n$ and P_n both vary with *n*. The probability $P_n = a/n$, for some $a \in (0,1,...,n)$ and f_{P_n} is larger when *a* is closer to $n/2$.

Now we consider the question of calculating the entropy for the clinical trial. If $P_n = p$ then we define the random variable:

$$H_n = -\left[p\log(p) + (1-p)\log(1-p)\right].$$

Define the asymptotic mean entropy as:

$$\lim_{n\to\infty} E\left[\frac{1}{n}\sum_{i=1}^{n} H_i\right] = \lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^{n} E\left[H_i\right].$$

The asymptotic mean entropy is thus a property of the trial sequence $\boldsymbol{C}$, not trial sets $\boldsymbol{S}^{(n)}$ or trials $\boldsymbol{T}^{(n)}$.

3.3. Results

Our results describe the relationship between the distribution of P_n and the entropy of the trial sequence, and also include a result about the variance of P_n for a certain allocation scheme.

LEMMA 1. *It is the case that if a clinical trial set targets the allocation ρ then*:

$$\lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^{n} E\left[P_i\right] = \rho .$$

THEOREM 1. *Optimal Entropy Theorem: Consider clinical trial sequence* ***C*** *that targets the allocation ρ. Then we have the following:*

a) The maximum value that the asymptotic mean entropy of any such sequence can take is equal to that of a clinical trial sequence where the allocation function f() is a coin with success probability ρ.

b) Another clinical trial sequence with the same target allocation will achieve the same maximum asymptotic mean entropy if and only if:

i) $\lim_{n\to\infty} \frac{1}{n-1}\sum_{i=1}^{n}\left(E[P_i] - \frac{1}{n}\sum_{i=1}^{n} E[P_i]\right)^2 = 0$

ii) $\lim_{n\to\infty} \frac{1}{n}\sum_{i=1}^{n} Var(P_i) = 0$

Note that Lemma 1 and Condition i) from Theorem 1 are not equivalent to

$\lim_{n\to\infty} E\left[P_n\right] = \rho$. This statement is stronger than Lemma 1 and Condition i) taken together.

This theorem shows when a clinical trial sequence with a known target allocation achieves optimal entropy asymptotically. It connects entropy, which is a measure of the randomness that an interfering investigator will experience, with properties of the clinical trial sequence which are easier to verify.

We now provide a simpler condition for a clinical trial allocation set to achieve optimal entropy.

COROLLARY 1. *Consider clinical trial sequence* ***C*** *that targets the allocation ρ. Then* ***C*** *will achieve the maximum asymptotic mean entropy if* $P_n \xrightarrow{P} \rho$ *, where the limit is in probability*.

THEOREM 2. *Let* $\{P_n\}$ *and* $\{Q_n\}$ *be the sequences of conditional treatment assignment probabilities corresponding to two different trial sequences that target the allocation ρ. If* $\sigma^2 < \tau^2$, $n \to \infty$ *and*:

$$\sqrt{n}\left(P_n - \rho\right) \underset{D}{\to} N(0, \sigma^2),$$

$$\sqrt{n}\left(Q_n - \rho\right) \underset{D}{\to} N\left(0, \tau^2\right),$$

$$E[\sqrt{n}\left(P_n - \rho\right)^2] \to \sigma^2,$$

$$E[\sqrt{n}\left(Q_n - \rho\right)^2] \to \tau^2,$$

then we have the following two results:

i) The asymptotic mean entropy of both trials is H(ρ) so each achieves the maximum entropy for that target allocation.

ii) *There exists $m \in N$ such that for all $n > m$, the mean entropy after n patients in the first trial exceeds the mean entropy after n patients in the second trial.*

This result shows that it is possible to rank the entropy of asymptotically optimal entropy designs when P_n for each design is asymptotically normal, which is often the case.

LEMMA 2. *Let* $\{P_n\}$ *and* $\{Q_n\}$ *be the sequences of conditional treatment assignment probabilities corresponding to two different doubly adaptive biased coin designs that differ only in the values of the randomization parameter* γ. *Let the value of the randomization parameter be larger for the design corresponding to sequence* $\{Q_n\}$. *Then if* $n \to \infty$:

$$\sqrt{n}\left(P_n - \rho\right) \underset{D}{\to} N(0, \sigma^2),$$

$$\sqrt{n}\left(Q_n - \rho\right) \underset{D}{\to} N\left(0, \tau^2\right), \text{ for some } \sigma^2 < \tau^2$$

We will use Theorem 2 and Lemma 2 to justify an assertion about the doubly adaptive biased coin.

3.4. Allocation Designs

We consider designs that target a fixed allocation known before the trial, e.g. equal allocation, such as the fair coin, the permuted block design (Rosenberger and Lachin, 2009), Efron's coin (Efron, 1971) and Wei's coin (Wei, 1978). We also consider response adaptive designs, where responses are used to change the allocation proportion usually in order to assign more patients to

the better treatment. We will consider doubly adaptive biased coin design (Hu and Zhang, 2004), efficient randomized adaptive design (Hu, Zhang and He, 2009) and Ivanova's urn design (Ivanova, 2003).

Fair Coin. The patients are assigned to treatment by flipping a fair coin, and assigning each patient to treatment A if the coin comes up heads. This procedure targets equal allocation, and the asymptotic variance of the treatment allocation proportion is 0.25, the largest of all treatment allocation schemes considered. This scheme achieves optimal entropy for any trial length, because the probability of treatment assignment is always 0.5.

Permuted Block. The patients are assigned sequentially in blocks of size $m = a + b$ by choosing a permutation of the a *A*'s and b *B*'s in a way where all permutations are equally likely to be chosen. An observer who knows the $\boldsymbol{D}^{(n-1)}$ and $f()$ in this context can try to make predictions about X_n. Clearly the trial sequence targets the allocation $a/(a+b)$ with zero asymptotic variance. Figure 2 shows histograms of P_n for permuted block design with $a = b = 3$. From Figure 2 we see that permuted block does not achieve optimal entropy, because, $P_{j \times m}$, corresponding to the final patient allocated in each block, is Bernoulli($a/(a+b)$), which has positive variance. Thus, the second condition of the Optimal Entropy Theorem is violated, since a positive fraction 1/(a + b) of the P_i will have the same positive variance. When $a = b = 3$ the asymptotic mean entropy for this design is 0.49, much lower than 0.69, the maximum entropy for a design targeting equal allocation. It is worth noting that if a and b are large, P_n will be closer to a point mass at the target allocation for most of the patients that are assigned, due to properties of the binomial distribution. Thus increasing $a + b$ will increase the asymptotic mean entropy for

this type of design. However, the maximum will never be achieved for fixed $a+b$, and in practice large values of $a+b$ are not used for this design.

Efron's Coin. The basic idea (Efron, 1971) is that as soon as the treatments become sufficiently imbalanced favouring one treatment, then the randomization is chosen to favour the other treatment in an attempt to balance more quickly while still incorporating randomization so that the physician can never be certain of the next treatment assignment. Choose a probability $\eta >$ 0.5. In a clinical trial with a target allocation of 0.5, the treatment allocation function is:

$$P_n = 0.5 \qquad \text{if } |N_{nA} - (n - N_{nA})| = 0,$$

$$P_n = 1-\eta \qquad \text{if } N_{nA} - (n - N_{nA}) > 0,$$

$$P_n = \eta \qquad \text{if } N_{nA} - (n - N_{nA}) < 0.$$

It has been shown (Markaryan and Rosenberger, 2010) that the asymptotic variance of N_{nA} / n approaches zero.

Efron's coin also does not have optimal entropy because P_{2n} converges the following attractor distribution (Markaryan and Rosenberger, 2010):

$$1-\eta \text{ with probability } \frac{1}{4\eta},$$

$$\frac{1}{2} \text{ with probability } \frac{2\eta-1}{2\eta},$$

$$\eta \text{ with probability } \frac{1}{4\eta}.$$

Clearly this distribution has positive variance. Since P_{2n} is bounded, its convergence implies convergence of moments, so condition ii) of the Optimal Entropy Theorem is violated.

The asymptotic mean entropy of Efron's coin is:

$$\frac{1}{4\eta}\left[(2\eta-1)\log 2-\left(\eta+2\eta^2\right)\log\eta-\left(1+\eta-2\eta^2\right)\log(1-\eta)\right].$$

For $\eta = 0.84$ Efron's coin has the same asymptotic mean entropy as the permuted block design with block of size 3 + 3.

Wei's Coin. This clinical trial allocation scheme targets the allocation 0.5. Let the discrepancy $D_n = \left[N_{nA} - (n - N_{nA})\right]/n$. Then

$$\Pr\left[X_n = A|\boldsymbol{D}^{(n-1)}, f()\right] = \Pr\left[X_n = A|D_n, f(\ )\right] = g(D_n),$$

where $g()$ is some non-increasing function with $g(x) = 1 - g(-x)$, for example, $(1-D_n)/2$ (Wei, 1978). This design was described in Example 3 in the introduction. Efron's coin is a special case of Wei's coin. Wei (1978) showed that the expected bias in such an experiment approaches zero asymptotically, and that $\sqrt{n}\left(D_n/n\right) \equiv \sqrt{n}\left(2N_{nA}/n - 1\right) \xrightarrow{D} N\left(0, 1/\left[1-4g'(0)\right]\right)$ when $g()$ is differentiable at zero. Then the asymptotic variance of the allocation proportion is always a positive real number. Of course, this result does not apply to Efron's coin where $g()$ is not continuous.

Wei's coin achieves optimal entropy when $g()$ is continuous on [-1, 1]. To see this note that Wei's coin always targets 0.5, and that $g(0.5) = 0.5$ by symmetry. Then by the continuous mapping theorem, P_n approaches 0.5 in probability, so by Corollary 1 optimal entropy is

achieved. However, note that the asymptotic variance of the allocation proportion for this design is positive when $g()$ is differentiable at zero, which is the case for Wei's suggested choice of $g()$. In comparison, the asymptotic variance of the allocation proportion for the Permuted Block design and Efron's coin is zero.

Doubly Adaptive Biased Coin (DABC). The doubly adaptive biased coin design (Hu and Zhang, 2004) allocates patient j to treatment A with probability $g(N_{(n-1)A}/(n-1), \hat{\rho})$, where $\hat{\rho}$ is the target proportion estimated from the data. We use the choice of $g(,)$ from Hu and Zhang (2004):

$$g(x,\hat{\rho}) = \frac{\hat{\rho}(\hat{\rho}/x)^{\gamma}}{\hat{\rho}(\hat{\rho}/x)^{\gamma} + (1-\hat{\rho})\left[(1-\hat{\rho})/(1-x)\right]^{\gamma}},$$
$$g(0,\hat{\rho}) = 1,$$
$$g(1,\hat{\rho}) = 0.$$

This $g(,)$ is chosen because it has several desirable properties (Hu and Zhang, 2004). The nonnegative number γ is a design parameter controlling the amount of randomization in the design. Let $\rho(p_A, p_B)$ be the target allocation proportion as a function of p_A and p_B, for example, $\rho(p_A, p_B) = \sqrt{p_B q_B}/\left(\sqrt{p_A q_A} + \sqrt{p_B q_B}\right)$ for inverse Neyman allocation (Ivanova, 2003), where $q_i = 1 - p_i$, $i = A, B$. Hu and Zhang (2004) give the following formula for the asymptotic variance, ω^2, of N_{nA}/n

$$\omega^2 = \frac{\omega_1^2}{1+2\gamma} + \frac{2(1+\gamma)}{1+2\gamma}\omega_2^2, \text{ where}$$
$$\omega_1^2 = \rho(p_1,p_2)\left[1-\rho(p_1,p_2)\right],$$
$$\omega_2^2 = \left(\frac{\partial\rho(p_1,p_2)}{\partial p_1}\right)^2 \frac{p_1 q_1}{\rho(p_1,p_2)} + \left(\frac{\partial\rho(p_1,p_2)}{\partial p_2}\right)^2 \frac{p_2 q_2}{1-\rho(p_1,p_2)}.$$

When $\gamma = 0$, the design is fully randomized, and the asymptotic variance is $\omega_1^2 + 2\omega_2^2$; when $\gamma = +\infty$ the design is deterministic, the asymptotic variance is ω_2^2 and is equal to the lower bound of the asymptotic variance of the allocation proportion. It was recommended (Hu and Rosenberger, 2005) to use the design with $\gamma = 2$. We prove the following result about DABC design:

The asymptotic variance of P_n for a trial sequence using the doubly adaptive biased coin design with the larger randomization parameter is larger than that with the trial sequence using the smaller randomization parameter.

Figure 2.3 shows histograms of P_n for response adaptive randomization designs with target allocation $\rho = 2/3$. Note that the means of P_n for each figure approach the target allocation $\rho = 2/3$. The DABC design achieves optimal entropy. The justification for this is similar to that of Wei's coin. Hu and Zhang (2004) showed that the joint distribution of $(N_{nA}/n, \hat{\rho})$ is asymptotically multivariate normal when standardized by $\sqrt{n}$. The Delta method can be used to show that P_n is also asymptotically normal. Thus it must converge to a point mass when not standardized. Then we can apply Corollary 1 to get the desired result. This result holds for all finite values of the randomization parameter γ. It is clear from Figure 2.3 that the variance of P_n is shrinking for this design as *n* grows. Note also the increasing normality of P_n for the DABC in Figure 2.3, as predicted by theory; Kolmogorov-Smirnov tests confirm this.

It is interesting that the randomization parameter γ in the DABC design, which does in fact affect the entropy of the trial in the finite sample case, actually has no effect on the asymptotic mean entropy of the trial. This follows directly from Corollary 1. The DABC design

achieves optimal entropy for all finite γ, which means that the DABC always has greater asymptotic mean entropy than designs that do not achieve optimal entropy, such as permuted block design. Figure 2.4 illustrates this phenomenon.

By combining Theorem 2 with Lemma 2, that, provided the first three moments of P_n exist for the DABC, increasing the randomization parameter does in fact decrease the entropy for the DABC in different sense: the mean entropy for the DABC with the smaller value of γ will eventually exceed that of the DABC design with the larger value of γ, even as both mean entropies approach the same limit.

An important question to answer is how to choose the randomization parameter γ in the DABC design. Hu and Zhang (2004) recommended $\gamma = 2$ because it yields a good trade-off between the amount of randomness the design provides and the variance of the allocation proportion. Our results show is that the best value of γ actually depends on the length of the trial. This is because when the trial is long, say 200-300 patients and power is an issue, we can see from Figure 2.4 that we would lose very little entropy if γ is increased to say, 6. However, this could shrink the asymptotic variance of the trial sequence by a factor of 2 or 3, which would add several percentage points of power. Similarly, if power is less of an issue and the trial is short, a smaller value of γ like 1 or 2 should be chosen so that there is enough randomness; the trial will not be long enough for the entropy to approach its maximum.

Efficient Randomized Adaptive Design (ERADE). The ERADE (Hu, Zhang and He, 2009) is a generalization of Efron's coin and can target any desirable allocation. The ERADE requires specifying a design parameter α, $0 < \alpha < 1$. As before, $\hat{\rho}$ is the estimated target allocation. Then

the next patient is assigned to treatment *A* with probability $\hat{\rho}\alpha$ if the allocation proportion exceeds $\hat{\rho}$; with probability ρ if the allocation proportion is equal to $\hat{\rho}$; and with probability $1-(1-\hat{\rho})\alpha$ if the allocation proportion exceeds the estimated target allocation. Hu, Zhang and He (2009) recommended using α in [0.4, 0.7]. This design achieves the lower bound of the asymptotic variance of the allocation proportion (Hu, Rosenberger and Zhang 2006). Efron's coin can be thought of as a special case of ERADE where $\rho = 1/2$ is known in advance.

ERADE does not achieve optimal entropy. To see this, note first that ERADE targets the allocation ρ, with three different coins that are each a fixed function of the estimated target allocation, so that P_n will converge to a discrete distribution with at most three point masses. Upon further inspection we see that the discrete attractor distribution will only have two point masses. This is because the mass placed on the second point mass, ρ, will approach zero. The reason for this is that the allocation proportion has an asymptotic normal distribution when properly standardized (Hu, Zhang and He, 2009), which means that probability that it is exactly equal to ρ must approach zero because the normal distribution has a continuous density. But P_n is only equal to the second point mass when the estimated target allocation is exactly equal to ρ. This is why the attractor distribution for P_n only has two point masses. Since its mean must approach ρ, and one point mass is larger than ρ and another is smaller, the discrete attractor distribution must have positive variance so Condition ii) of the Optimal Entropy Theorem is violated. Because the two point masses are relatively far apart, ERADE tends to have the lowest mean entropy of the response adaptive design we considered.

Ivanova's urn. The design from Ivanova (2003) is implemented by an urn with three different kinds of balls: immigration, treatment *A*, and treatment *B*. Balls are drawn from the urn sequentially. If the ball drawn is immigration, one ball is added to the urn for each treatment and no patient is assigned. If the ball drawn is one of the treatment balls, the next patient is assigned that treatment and the ball is replaced. If the patient fails, one ball from that treatment is removed from the urn. If the patient does not fail, the urn composition remains unchanged. This design achieves lower bound of the treatment allocation proportion variance (Hu and Rosenberger, 2003) but only targets one allocation.

Ivanova's urn design also does not achieve optimal entropy. To see this, note that the mean number of balls of type *A* or *B* will approach $Z_0/(1-p_A)$ or $Z_0/(1-p_B)$ respectively (Ivanova, 2003), where Z_0 is the initial number of immigration balls. Since the lower bound for the number of balls of any type is zero, this means that the number of balls in the urn must eventually be less than some upper bound *U* with some minimum probability. This means that the urn proportion of type *A* balls must have positive variance, since there is a lower bound on the transition probabilities between different consecutive values of this allocation proportion when the urn is bounded by *U*. Since the probability of assigning the next patient to *A* is clearly not constant as a function of the number of type *A* balls there must be a lower bound on the average variance of P_n, so Condition ii) of the Optimal Entropy Theorem is violated. Note that in Figure 2.3, the mean approaches $\rho = 2/3$, but the variance does not approach zero. The variance is still rather small, however, so the urn has a reasonable amount of entropy.

3.5. Conclusions

In this work, for an allocation design, we have defined the random variable P_n and shown how the distribution of this random variable is connected to the asymptotic mean entropy of the sequence of assignments for that design. We proved the Optimal Entropy Theorem, which states that a coin with success probability equal to the target allocation always achieves the maximum amount of entropy, and gives necessary and sufficient conditions for a clinical trial sequence that targets that allocation to achieve this maximum. Then we applied this theorem to existing designs to show which clinical trial designs achieve this optimum amount of entropy. We have shown that when P_n is asymptotically normal there is a direct connection between its variance and asymptotic mean entropy, and have demonstrated more generally that entropy often decreases with the variance of P_n. Theorem 2 and Lemma 2 together offer, for the first time, a clear explanation of why increasing the randomization parameter in the doubly adaptive biased coin design decreases the randomization of the design. Theorem 1 further shows that the choice of this randomization parameter has no effect on the asymptotic mean entropy.

Some implications of our findings are counterintuitive. The first is that, if a trial set targets the allocation 0.5 and achieves optimal entropy, then, as the trial becomes longer, the second half of the trial will eventually contribute *at least as much* to the mean entropy than the first half. To see why, note that if the trial achieves optimal entropy for $\rho = 0.5$ then after a certain *n* the average of all P_i must have means arbitrarily close to 0.5 and variances arbitrarily close to zero. Since 0.5 is the point with maximum entropy, the entropy from the second part of the trial must be at least as great as from the first part. This means that even as the investigators gathers more data about the history of the trial, their ability to predict the next treatment assignment will, in fact, decrease on average. This is a direct consequence of both conditions of the Optimal Entropy

Theorem. In fact, for any target allocation, the second half of an optimal entropy trial may eventually contribute more to the mean entropy than the first half but this is only certain for $\rho = 0.5$. The reason this does not necessarily hold for trial sequences with arbitrary ρ is that the mean of P_n may move from 0.5 to ρ more slowly than the variance shrinks.

An interesting issue that warrants further investigation is the relationship between the variance of P_n and the asymptotic variance of N_{nA}/n. It is clear that the allocation scheme from Example 2 in Section 2 has the minimum possible asymptotic variance of N_{nA}/n, yet P_n always has the maximum possible variance. Now consider a trial designed as follows: a fair coin is flipped. If it is heads, then the treatments are assigned: *AAABAAAB*… If the coin lands tails, the treatments are assigned: *BBBABBBA*… Random variable P_n still has the maximum possible variance, yet the asymptotic variance of the allocation proportion is now infinite. This shows that if the variance of P_n is large, there is very little that can be said about the asymptotic variance of the allocation proportion. However, if the variance of P_n is very small, or even approaches zero, as in the case of optimal entropy, it is not known if greater restrictions can be placed on the asymptotic variance of the allocation proportion. If a lower bound for the asymptotic variance of an optimal entropy trial could be established, this would be an important step in understanding what an optimal sequential clinical trial should look like. It is not known if there is an optimal entropy design that achieves the lower bound of the asymptotic variance for asymptotically normal allocation proportions when the target allocation is not known in advance (ERADE achieves this lower bound, but it is not optimal entropy). Using functions that have unbounded slope in an neighbourhood containing zero, we have found an optimal entropy design based on

Wei's Coin that targets equal allocation and appears to have zero asymptotic variance, but this fact remains to be proved.

Figure 3.1. Density of P_n for designs. Consider the examples given in Section 2 with the total sample size n = 20 and 80.

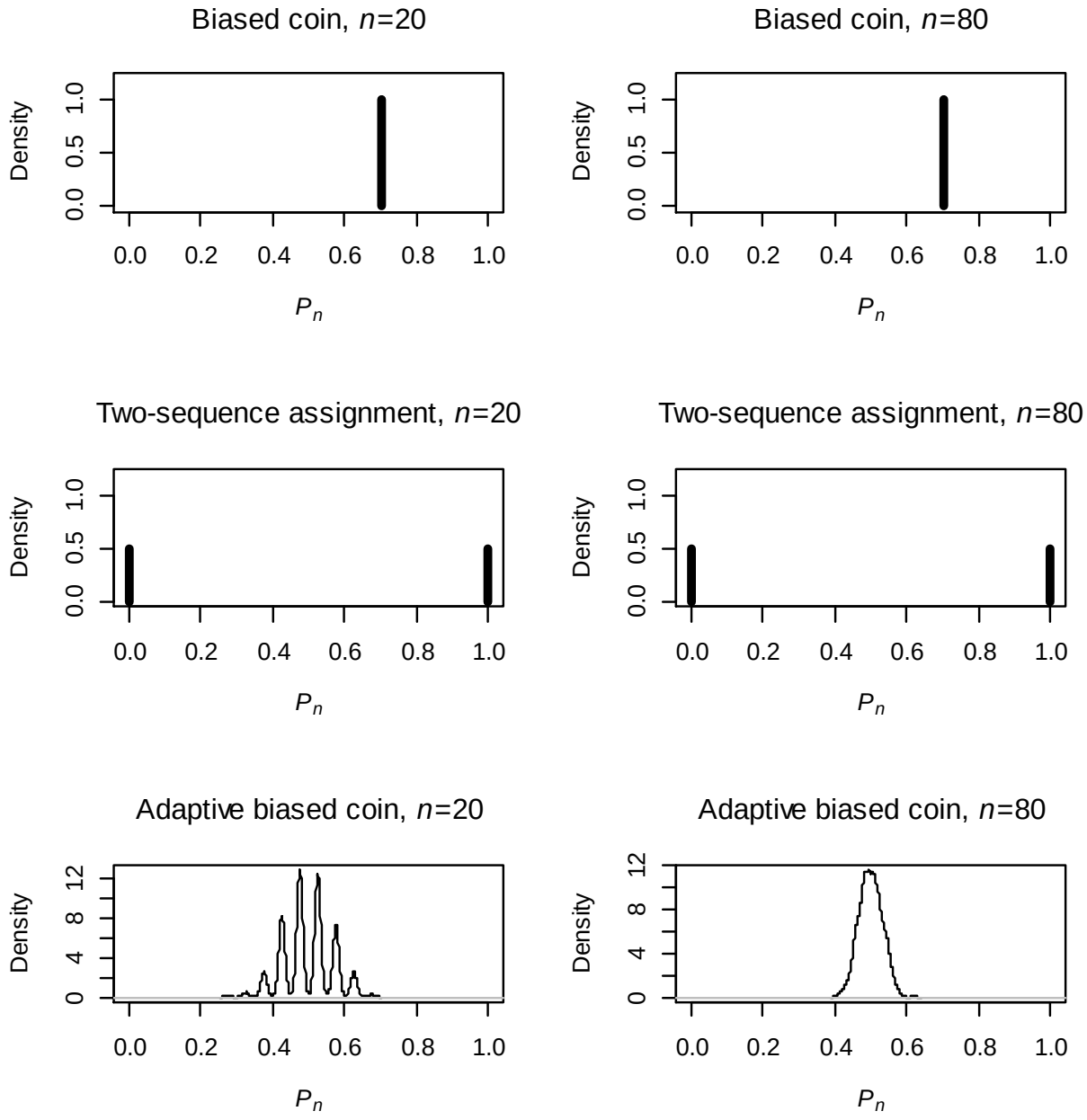


Figure 3.2. Density of P_n for designs in Section 4 with fixed target allocation. Permuted block design with blocks of size 6 (3+3), Efron's coin with $\eta = 0.75$ and Wei's coin with $g(x) = 1 - x$. For each design, three different values of total sample size *n* are considered.

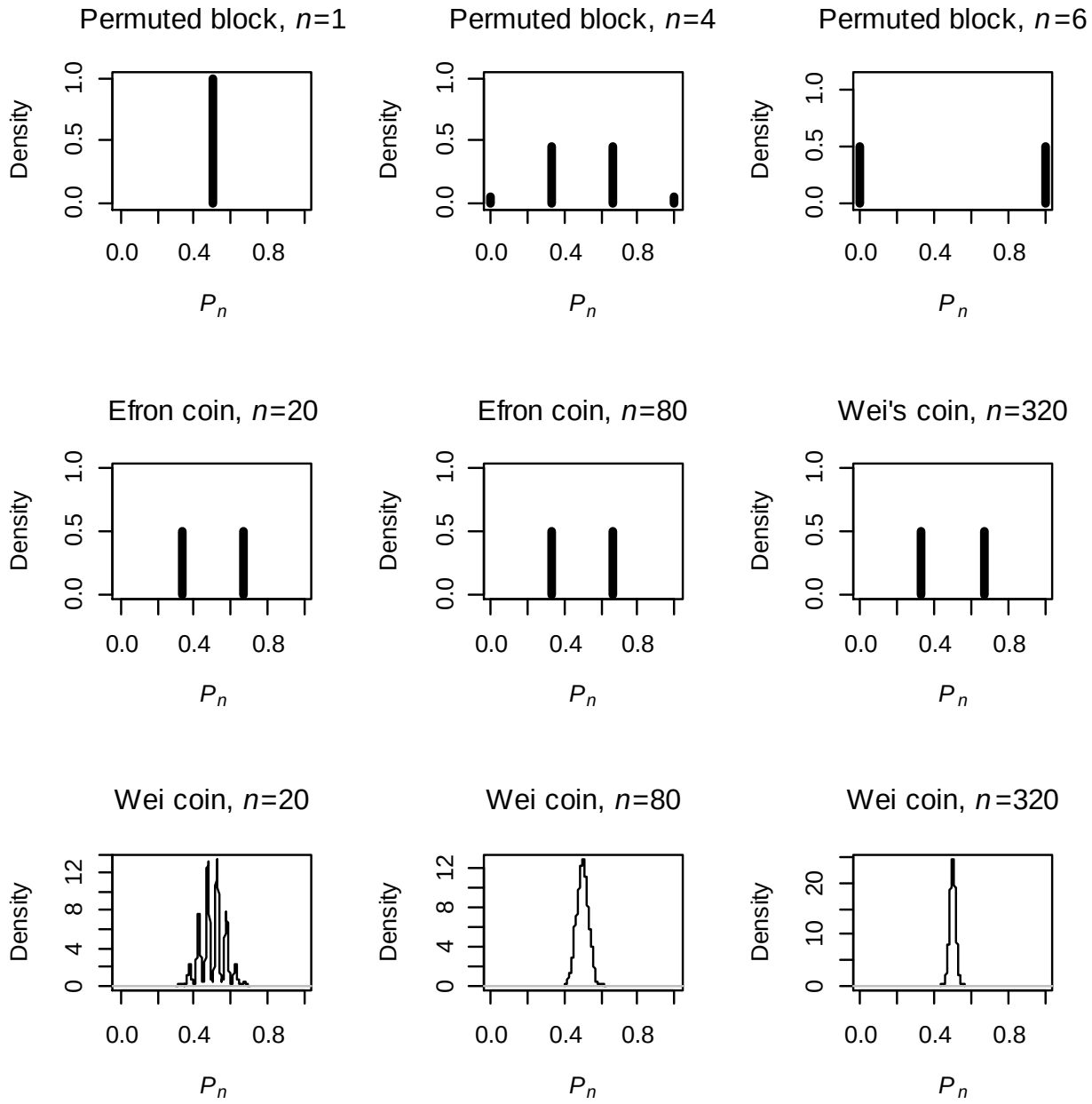


Figure 3.3. Density of P_n for response adaptive designs from Section 4. For all designs, p_A = 0.50, $p_B = 0.75$ and $\rho = 2/3$. The DABC uses $\gamma = 8$; the ERADE uses $\alpha = 0.5$; Ivanova's urn design uses an initial urn composition of 10 of each type of ball.

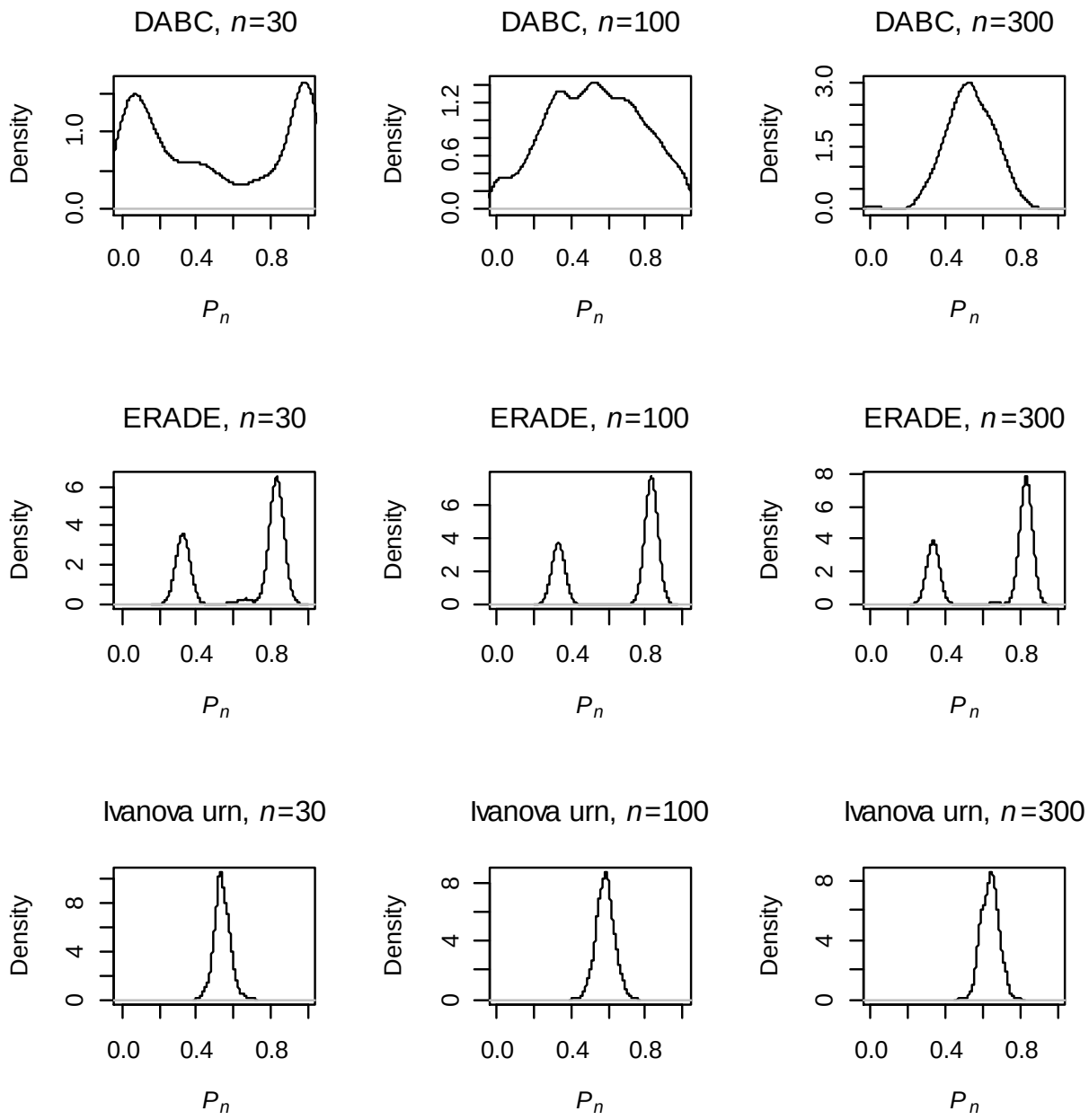
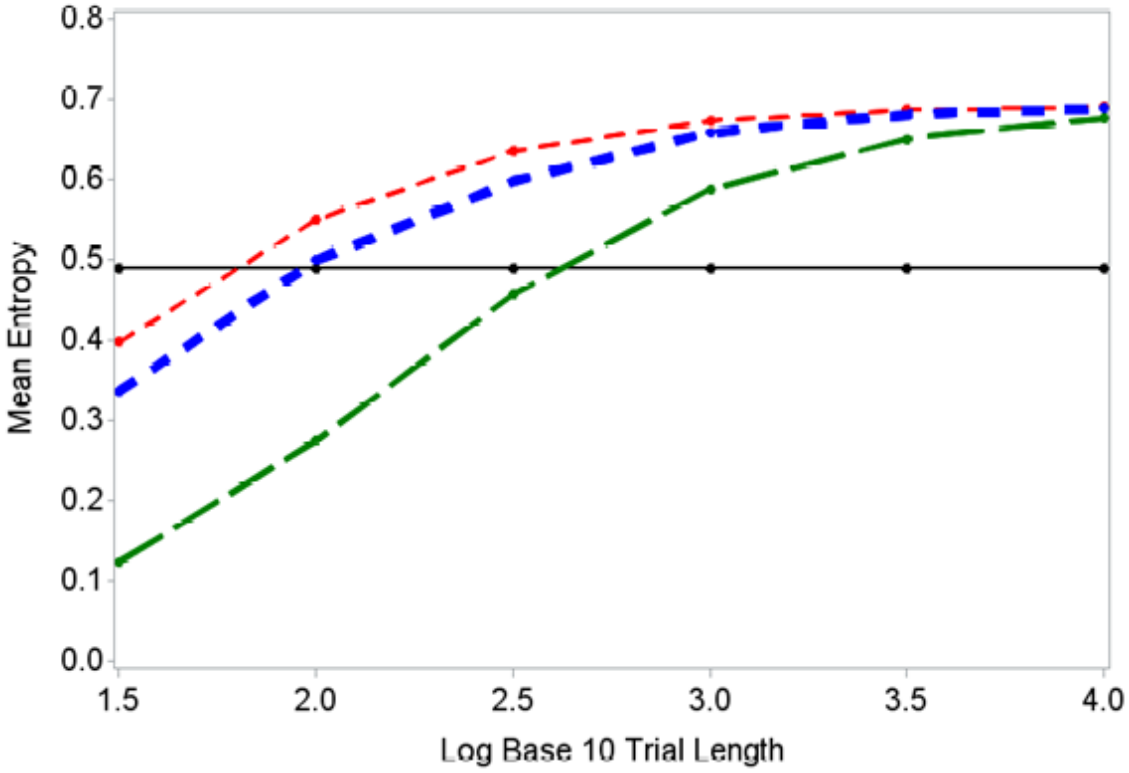


Figure 3.4. Asymptotic mean entropy. Consider permuted block design of size 6 (3+3) (solid line at 0.49) and the Doubly Adaptive Biased Coin design with $p_A = 0.44$, $p_B = 0.56$, γ=2 (top dashed line), γ=10 (middle dashed line), and γ=100 (bottom dashed line). Both designs target $\rho = 1/2$. The figure illustrates that the DABC achieves optimal entropy for all values of γ, and that larger values of gamma yield less entropy for smaller *n*. The permuted block does not achieve optimal entropy.



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CHAPTER 4: THE BROWNIAN DISTANCE COVARIANCE IN SURVIVAL ANALYSIS

4.1 Introduction.

The problem of relationship detection is one of the oldest questions in statistics, dating back to the nineteenth century, before the existence of modern statistical theory. The most lasting contribution from this time period is linear regression, a method that is still in use today. Its optimality was first justified using the Gauss Markov Theorem, and later UMVU estimation. In addition to being optimal for detecting a straight line relationship, simple linear regression also has the power to detect other monotone relationships, and even some relationships that are not monotonic. The technique can be augmented by adding higher order terms.

However, there is still a need within the discipline to develop relationship detection techniques for situations when very little about the form of the relationship is known. In 2009, Szekely and Rizzo proposed the Brownian Distance Covariance, which uses a simple statistic to detect whether two random variables are independent. This method is based on the relationship between the difference of the joint and product marginal characteristic functions and a trigonometric weight function. This technique can detect dependencies that are more complex than simple functional relationships with noise added. It can also be used to detect relationships between sets of vectors. In 2011, Reshef and others proposed the MINE statistic, which uses a series of grids to select a relationship based on mutual information. This technique is based on ranks and has lower power for moderate sample sizes. The authors also claim that this technique has a very similar power for different relationships with the same amount of noise.

Survival analysis has long employed the Cox model to test for differences among covariates. This model allows for the testing of whether covariates are associated with time to event. One of the strengths of this model is that the baseline hazard function need not be specified. However, this model relies on the proportional hazards assumption, which may not always hold. For example, one way this assumption may be violated is if the two survival curves cross for certain values of the covariate. However, even in this case meaningful differences in survival time may exist. The Aalen additive risk model (McKeague and Sasieni, 1994) is an alternative that avoids this problem but is more limited in the number of covariates that it can handle. Thus the discipline might benefit from new approaches to detecting survival time differences. Here we propose using the Brownian Distance Covariance to search for relationships in survival data that may not be detectable using the Cox model. This requires modifying the Brownian Distance Covariance so that it can accommodate right-censored data. There are two modifications we propose to the Brownian Distance Covariance to accommodate the right censoring. The first is to use the fact that, if the covariate and censoring time are independent, then the conditional distribution of the failure time given the covariates and the censoring time is unit exponential. The second approach involves imputing the censored failure times by sampling from the known failure times when each failure time is weighted by the standard cumulative hazard function. We proceed to compare each of these two approaches to the Cox Model, which is designed to detect monotone relationships. We also compare these existing approaches to the method used by Kwak in her 2006 thesis. Kwak's method is based on the convergence of cumulative hazard functions to a Brownian Bridge. We also compare the first two approaches to linear regression as well, as they are based on complete data.

4.2 Methods.

We will now describe Brownian Distance Covariance in detail (Szekely and Rizzo, 2009). Let f_X, f_Y , $f_{X,Y}$ denote the marginal and joint characteristic functions of two continuous random vectors in $\mathbb{R}^p$ and $\mathbb{R}^q$. Let $V(X,Y,w) = \int_{R^{p+q}} | f_{X,Y}(t,s) - f_X(t) f_Y(s) |^2 \, w(t,s,p,q)dtds$, where w is a positive weight function.

For certain reasons we want a non-integrable trigonometric weight function. This leads to distance correlation:

$$R_w = \frac{V(X,Y,w)}{\sqrt{V(X,X,w) * V(Y,Y,w)}}.$$

Now let

$a_{kl}=|X_k-X_l|_p$ $b_{kl}=|Y_k-Y_l|_q$,

$A_{kl}=a_{kl}-a_{k.}-a_{.l}+a_{..}$ and $B_{kl}= b_{kl}-b_{k.}-b_{.l}+b_{..}$ and the "." indicates a marginal mean.

Then $V^2_n(X,Y)= \frac{1}{n^2}\sum_{k,l=1}^{n} A_{kl}B_{kl}$

V^2_n and R^2_n tend almost surely to their theoretical values, R^2 and V^2. Both are invariant under affine transformation of their arguments. There are two special values:

R^2 =0 if and only if X an Y are independent,

R^2=1 implies strict linear dependence,

nV^2_n has two different limit distributions in the case of dependence and independence.

We now discuss the first imputation method for the Brownian Distance Covariance in more detail. The idea is to test for independence of the failure times and a set of covariates by first assuming that the covariates are independent of them. As usual, the censoring time is assumed independent of the failure time. Further assume that this independence holds for the covariates. Also, let X_i denote the minimum of the failure time and the censoring time. Also let δ_i denote an indicator equal to 1 when X_i is the failure time. The first part of this idea is that the

cumulative hazard as a function of the failure time is exponential given the covariates. That is, we generate

$$T_i^{'} = \delta_i \Lambda^{'}(T_i) + (1-\delta_i)\exp(1)(T)|T > \Lambda^{'}(C_i).$$

Here T_i is the observed failure time, C_i is the censoring time $\Lambda^{'}$ is the cumulative hazard and T is a unit exponential random variable. This can be generated with several thousand replications to create a distribution of Brownian Distance Covariance values using replications from the data when they are compared to the covariate vectors. Then the observed value of the Brownian Distance Covariance can be compared to the significance level from this distribution. The reason that this bootstrapping is necessary is that the null distribution of the Brownian Distance Covariance is unknown and depends on the underlying distribution, so that the null distribution must be generated experimentally. One issue that arises from this technique is whether the power would be increased with the number of covariates that are not independent of the failure time, if each covariate that was not independent carried the same strength of relationship. This is a general question related to the structure of the Brownian Distance Covariance that can be addressed experimentally to a certain extent.

The second approach to imputation with the Brownian Distance Covariance involves, for each censored observation, sampling from the remaining failure times that are greater than the observation when the sampling of each failure time is weighted by the difference in the standard nonparametric survival curve estimate at that failure time.

Kwak's method, (Kwak, 2006) involves comparing the standardized supremum of the difference of a standard cumulative hazard Nelson-Aalen estimator with that of a cumulative

hazard analogue derived from an empirical process that incorporates covariate information in a Vapnik-Chervonenkis class of sets in the covariate space. The test statistic is:

$$T_n^{RC} = \sqrt{n}\max_{t\in[0,\tau] I_z \in Z_\epsilon} |\Lambda_n(t) - \Lambda_n^Z(t,z)|,$$

Where

$\Lambda_n(t)$ is the usual Nelson Aalen estimator for the cumulative hazard function and

$$\Lambda_n^Z(t,z) = \int_0^t \frac{\boldsymbol{P_n}\Delta 1_{[M\le ds, Z\le z]}}{\boldsymbol{P_n} 1_{[M\ge s, Z\le z]}},$$

where $\boldsymbol{P_n}$ represents an empirical process, *M* represents the event and *Z* represents the covariate. The test statistic converges to the linear functional of three Brownian Bridges, one of which is independent of the other two.

To implement the simulations, the covariates were generated first, and then the survival times and censoring times were generated independently conditional on the covariate vector. The covariate vector was generated from a Weibull(1,10). Let *cv* denote the covariate vector. The failure time vector was chosen from one of the following five:

6+0.5*$cv + \epsilon$ where $\epsilon\ is\ N(0, noise = 3)$

Uniform(min(*cv*), max(*cv*))+ ϵ

$e^{cv/5} + \epsilon$

$\sin(2\pi(cv)/\sqrt{4 * var(cv)}) + \epsilon$

$2((cv - mean(cv))/\sqrt{var(cv)})^2 + \epsilon$

The noise level was set to three and there were two censoring levels indicated. The first, 50%, was generated by re simulating the failure times and taking the minimum. The second, 20%, was generated separately for each type of failure time by generating a censoring time with a constant added to the formula for generating the failure time so that the target censoring rate was achieved.

4.3. Results.

Consult Tables 1-6 for the power calculations comparing the different methods. For the second imputation method, the Brownian Distance Covariance tends to outperform the Cox model and linear regression for the parabolic and sinusoidal relationships, while the Cox model performs better for the monotone relationships. The Cox model tends to be more powerful than Kwak's Method except when the relationship is sinusoidal. Kwak's method appears to be less powerful than Brownian Distance Covariance Imputation, and linear regression under the first imputation method appears to be more powerful than the Brownian Distance Covariance.

4.4 Conclusions.

The Brownian Distance Covariance appears to be a superior method to the Cox model for detecting nonlinear relationships. The superiority of the Brownian Distance Covariance to linear regression depends on the imputation method used. Whether the Brownian Distance Covariance is superior to the Cox Model at detecting a single related covariate when there are multiple covariates being tested simultaneously is an important question that remains to be answered.

Table 4.1. Power calculations for both imputation methods and heavy censoring.

Relationship	Cox model	Kwak's	BDC #1	Linear Reg #1	BDC #2	Linear Reg #2
Noise	0.05	0.06	0.05	0.95	0.06	0.04
Linear	0.98	0.30	0.52	0.88	0.93	0.94
Exponential	0.81	0.20	0.75	0.97	0.35	0.31
Parabolic	0.75	0.45	0.89	0.35	0.93	0.45
Sinusoidal	0.09	0.19	0.61	0.08	0.85	0.18

Table 4.2. Power calculations for both imputation methods and light censoring.

Relationship	Cox model	Kwak's	BDC #1	Linear Reg #1	BDC #2	Linear Reg #2
Noise	0.05	0.06	0.05	0.97	0.06	0.04
Linear	1	0.39	0.59	0.92	0.96	0.94
Exponential	0.88	0.32	0.86	0.97	0.46	0.39
Parabolic	0.79	0.55	0.95	0.39	0.96	0.62
Sinusoidal	0.12	0.29	0.77	0.08	0.97	0.28

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APPENDIX 1.1 TRANSITION PROBABILITIES FOR THE MARKOV PROCESS

Though we have two processes corresponding to the two treatment arms, it is sufficient to describe the behavior of a Markov process corresponding to a single treatment arm with success rate of p, $q = 1 - p$. In similar derivations in Ivanova et al. (2001) and Ivanova (2003) the state that the process is in was a function of the number of balls currently in the urn. In the second order urn, the state that the process is in is determined by the response of the previous patient and the number of balls currently in the urn. The initial urn contains one ball of each type. Assume that one patient has been already treated and response observed. If the response was a success, $X_1 = 1$, the Markov process starts at the state (1,1), if response was a failure, $X_1 = 0$, the Markov process starts at the state (0,1). Assume that the process is at the state $(0,m)$, $m > 0$, at time t. The following transitions are possible in time Δt:

$$(0,m) \to (0,m-1) \text{ with rate } mp\Delta t$$
$$(0,m) \to (0,m) \text{ with rate } mq\Delta t$$
$$(0,m) \to (0,m+1) \text{ with rate } a\Delta t$$

Similarly, if the process is in the state $(1,m)$, $m > 0$, at time t, the transitions in time Δt are:

$$(1,m) \to (1,m-1) \text{ with rate } mq\Delta t$$
$$(1,m) \to (1,m) \text{ with rate } mp\Delta t$$
$$(1,m) \to (1,m+1) \text{ with rate } a\Delta t$$

Let $p_{0,m}(t)$ equal the probability of being at state $(0,m)$ at time t, and $p_{1,m}(t)$ equal the probability of being at state $(1,m)$ at time t. To obtain backward equations we consider all possible ways to get to states (0,m) and (1,m) by time t:

$$
\begin{aligned}
&(1, m+1) \to (0, m) \text{ with rate } (m+1)q\Delta t,\\
&(0, m-1) \to (0, m) \text{ with rate } a\Delta t,\\
&(0, m) \to (0, m) \text{ with rate } 1 + mq\Delta t - m\Delta t - a\Delta t,\\
&(0, m+1) \to (1, m) \text{ with rate } (m+1)p\Delta t,\\
&(1, m-1) \to (1, m) \text{ with rate } a\Delta t,\\
&(1, m) \to (1, m) \text{ with rate } 1 + mp\Delta t - m\Delta t - a\Delta t.
\end{aligned}
\tag{2}
$$

Define generating functions

$$
G_0(t, z) = \sum_{m=0}^{\infty} p_{0,m}(t) z^m, \quad G_1(t, z) = \sum_{m=0}^{\infty} p_{1,m}(t) z^m \,. \tag{3}
$$

The system of partial differential equations (1) and its initial and boundary conditions are obtained from (2) and (3).

APPENDIX 1.2 TELESCOPING PROPERTY OF THE URN

Define $a_{j,m} = \{z_1(j)+m\}\left\{\prod_{k=0}^{m}(z_1(j)+z_2(j)+1+2k)\right\}^{-1}$, $m \geq 0$. We would like to show that $\sum_{k=m+1}^{\infty} a_{j,k} \leq a_{j,m}$. We first show that, $a_{j,m+1}/a_{j,m} \leq 0.5$. This ratio is

$$\frac{a_{j,m+1}}{a_{j,m}} = \frac{z_1(j)+m+1}{\prod_{k=0}^{m+1}\{z_1(j)+z_2(j)+1+2k\}}\left\{\frac{z_1(j)+m}{\prod_{k=0}^{m}[z_1(j)+z_2(j)+1+2k]}\right\}^{-1}$$

$$= \frac{z_1(j)+m+1}{\{z_1(j)+z_2(j)+1+2(m+1)\}\prod_{k=0}^{m}\{z_1(j)+z_2(j)+1+2k\}}\left\{\frac{z_1(j)+m}{\prod_{k=0}^{m}[z_1(j)+z_2(j)+1+2k]}\right\}^{-1}$$

$$= \frac{z_1(j)+m+1}{\{z_1(j)+m\}\{z_1(j)+z_2(j)+2m+3\}}$$

$$= \frac{1}{(z_1(j)+z_2(j)+2m+3)} + \frac{1}{(z_1(j)+m)(z_1(j)+z_2(j)+2m+3)} \leq \frac{1}{4}+\frac{1}{4} = \frac{1}{2},$$

because all terms are nonnegative and $z_1(j)+m \geq 1$.

The geometric sequence 0.5^n has the property that the sum of all terms beyond the *m*th term is equal to the *m*th term. Then, $a_{j,m+k} < (a_{j,m})(0.5)^k$ and therefore $\sum_{k=m+1}^{\infty} a_{j,k} \leq a_{j,m}$.

APPENDIX 2: PROOFS OF LEMMAS 1 AND 2 AND THEOREMS 1 AND 2.

Proof of Lemma 1. Clearly when a trial sequence targets ρ, $E[N_{nA}/n] \to \rho$ because N_{nA}/n has compact support. Note

$$\frac{N_{nA}}{n} = \frac{1}{n}\sum_{i=1}^{n} I\left(X_i = A\right) \Rightarrow E\left[\frac{N_{nA}}{n}\right] = \frac{1}{n}\sum_{i=1}^{n} Pr\left(X_i = A\right).$$

Also since

$$f_{P_n}\left(p\right) = \sum_{\boldsymbol{T}^{(n-1)} \in \boldsymbol{S}^{(n-1)}} I(\Pr\left(X_n = A|\boldsymbol{D}^{(n-1)}, f()\right) = p)\Pr(\boldsymbol{T}^{(n-1)}) .$$

We have

$$\begin{aligned}
\mathrm{E}\left[P_n\right] &= \int_0^1 p \sum_{\boldsymbol{T}^{(n-1)} \in \boldsymbol{S}^{(n-1)}} I\left[\Pr\left(X_n = A|\boldsymbol{D}^{(n-1)}, f(\ )\right) = p\right]\Pr\left(\boldsymbol{T}^{(n-1)}\right)dp \\
&= \sum_{\boldsymbol{T}^{(n-1)} \in \boldsymbol{S}^{(n-1)}} \left\{\Pr\left(\boldsymbol{T}^{(n-1)}\right)\int_0^1 pI\left[\Pr\left(X_n = A|\boldsymbol{D}^{(n-1)}, f(\ )\right) = p\right]dp\right\} \\
&= \sum_{\boldsymbol{T}^{(n-1)} \in \boldsymbol{S}^{(n-1)}} \Pr\left(X_n = A|\boldsymbol{D}^{(n-1)}, f(\ )\right)\Pr\left(\boldsymbol{T}^{(n-1)}\right) \\
&= \Pr\left(X_n = A\right).
\end{aligned}$$

And from this the desired result that $\lim_{n\to\infty}\frac{1}{n}\sum_{i=1}^{n} E\left[P_i\right] = \rho$ follows.

Proof of Lemma 2.

Rewrite the treatment allocation function for the doubly adaptive biased coin as:

$$g_\gamma(x, \hat{\rho}) = \frac{\hat{\rho}}{\hat{\rho} + (1-\hat{\rho})\left(\frac{1/\hat{\rho} - 1}{1/x - 1}\right)^\gamma}.$$

Choose $h(x, \hat{\rho}) = x + \hat{\rho}$. We see from p. 273 (Hu and Zhang, 2004) that :

$$(\sqrt{n}(x-\rho),\sqrt{n}(\hat{\rho}-\rho)) \xrightarrow{D} N(0,\Lambda),$$

where

$$\Lambda = \begin{pmatrix} \frac{\sigma_1^2}{1-2\lambda} + \frac{2\omega^2\sigma_3^2}{(1-\lambda)(1-2\lambda)} & \frac{\omega\sigma_3^2}{1-\lambda} \\ \frac{\omega\sigma_3^2}{1-\lambda} & \sigma_3^2 \end{pmatrix}$$

and

$$\sigma_1^2 = \rho(1-\rho),$$
$$\sigma_3^2 = \frac{p_1(1-p_1)}{\rho}(\frac{\partial\rho}{\partial p_1})^2 + \frac{p_2(1-p_2)}{1-\rho}(\frac{\partial\rho}{\partial p_2})^2,$$
$$\lambda = \frac{\partial g_\gamma}{\partial x}|_{\rho,\rho},$$
$$\omega = \frac{\partial g_\gamma}{\partial \hat{\rho}}|_{\rho,\rho}.$$

Thus the asymptotic normality of $\sqrt{n}\left(P_n-\rho\right)$ and $\sqrt{n}\left(Q_n-\rho\right)$ follow immediately from the Delta method.

We also see from the presentation of the Delta method on p. 61 of Lehmann and Casella that:

$$(\sqrt{n}[g_\gamma(x,\hat{\rho})-g_\gamma(\rho,\rho)],\sqrt{n}[h(x,\hat{\rho})-h(\rho,\rho)])$$

tends in law to $N(0,\sum)$, where:

$$\sum = B\Lambda B^T \text{ and } B = \begin{pmatrix} \frac{\partial g_\gamma}{\partial x} & \frac{\partial g_\gamma}{\partial \hat{\rho}} \\ \frac{\partial h_\gamma}{\partial x} & \frac{\partial h_\gamma}{\partial \hat{\rho}} \end{pmatrix}.$$

This is because the matrix *B* is nonsingular, due to the choice of *h*() (see computations of *B* below). We know from the Cramer-Wold device that the marginal distributions of

$$(\sqrt{n}[g_\gamma(x,\hat{\rho}) - g_\gamma(\rho,\rho)], \sqrt{n}[h(x,\hat{\rho}) - h(\rho,\rho)])$$

tend to the marginal distributions of $N(0,\sum)$.

Thus, part i) of Claim 3 follows from part i) of Claim 2. Now we show part ii). It is known that the variances of the variables in the bivariate normal density are just the diagonal elements of $\sum$. Thus we see from matrix multiplication that the asymptotic variance of $\sqrt{n}[g_\gamma(x,\hat{\rho}) - g_\gamma(\rho,\rho)]$ (i.e. the first element of $\sum$) does not depend on the bottom half of *B*. To compute this element explicitly, we first note that because we are evaluating the Jacobian matrix at $x = \hat{\rho} = \rho$, the first row of *B* is equal to $(\lambda,\omega)^T$. Then we use maple, specifically the "multiply" command for matrices and the "simplify" command for the resulting algebraic expression to obtain: $\frac{\lambda^2\sigma_1^2}{1-2\lambda} + \frac{\omega^2\sigma_3^2}{1-2\lambda}$. To verify that this quantity is strictly monotone increasing in γ we compute $\frac{\partial g_\gamma}{\partial x}$ and $\frac{\partial g_\gamma}{\partial \hat{\rho}}$ explicitly using calculus.

$$\frac{\partial g_\gamma}{\partial x} = \frac{-\hat{\rho}(1-\hat{\rho})(\frac{1}{\hat{\rho}}-1)^\gamma \gamma \left(\frac{1}{1/x-1}\right)^{\gamma-1} (\frac{1}{1-x})^2}{(\hat{\rho}+(1-\hat{\rho})\left(\frac{1/\hat{\rho}-1}{1/x-1}\right)^\gamma)^2} = \frac{-\hat{\rho}(1-\hat{\rho})\gamma T(1/x-1)(\frac{1}{1-x})^2}{(\hat{\rho}+(1-\hat{\rho})T)^2},$$

where $T = \left(\frac{1/\hat{\rho}-1}{1/x-1}\right)^{\gamma}$. Similarly,

$$\frac{\partial g_{\gamma}}{\partial \hat{\rho}} = \frac{(\hat{\rho}+(1-\hat{\rho})\left(\frac{1/\hat{\rho}-1}{1/x-1}\right)^{\gamma}) - \hat{\rho}(1-\left(\frac{1/\hat{\rho}-1}{1/x-1}\right)^{\gamma} - \frac{\gamma}{\hat{\rho}}\left(\frac{1/\hat{\rho}-1}{1/x-1}\right)^{\gamma})}{(\hat{\rho}+(1-\hat{\rho})\left(\frac{1/\hat{\rho}-1}{1/x-1}\right)^{\gamma})^2} = \frac{(1+\gamma)T}{(\hat{\rho}+(1-\hat{\rho})T)^2}$$

,

$x = \hat{\rho} = \rho$ and hence $T = 1,$ so we have $\lambda = -\gamma$ and $\omega = 1+\gamma$. Then the first element of Σ becomes $\frac{\gamma^2\sigma_1^2}{1+2\gamma} + \frac{(1+\gamma)^2\sigma_3^2}{1+2\gamma}$. We need to show that this is monotonically increasing in γ. Note that it is a positive linear combination of two other functions, $\frac{\gamma^2}{1+2\gamma}$ and $\frac{(1+\gamma)^2}{1+2\gamma}$. If we can show that each of these functions is monotonically increasing in γ then it will follow that the first element of Σ is as well. This in turn is equivalent to showing that the logarithm of each function is monotonically increasing in γ. When $\gamma > 0$

$$\log(\frac{\gamma^2}{1+2\gamma}) = 2\log(\gamma) - \log(1+2\gamma),$$

$$\frac{d}{d\gamma}[2\log(\gamma) - \log(1+2\gamma)] = \frac{2}{\gamma} - \frac{2}{1+2\gamma} > 0,$$

$$\log(\frac{(1+\gamma)^2}{1+2\gamma}) = 2\log(1+\gamma) - \log(1+2\gamma),$$

$$\frac{d}{d\gamma}[2\log(1+\gamma) - \log(1+2\gamma)] = \frac{2}{1+\gamma} - \frac{2}{1+2\gamma} > 0.$$

Thus we have shown that a larger value of γ results in a larger asymptotic variance of $\sqrt{n}(P_n - \rho)$. *QED*

Proof of Theorem 1.

a) Consider function $H(x)=-\left[x\log(x)+(1-x)\log(1-x)\right]$. $H(x)$ is strictly concave in (0,1) since its second derivative is strictly negative. Using Jensen's inequality (Casella and Berger, p. 190) we get $H(E[x])\geq E[H(x)]$ and that equality holds only when concavity is not strict, or when $P(X=E[X])=1$. Since concavity is strict, we must have that the density is a point mass with probability 1. There is a special consideration for a density that assigns mass to the points 0 or 1, which are not in (0,1). However, because $H(0)=0=H(1)$, we know that such a density could never maximize the entropy, since $H(x)>0$ for all $x\in(0,1)$. Thus we see that the maximum asymptotic mean entropy can be achieved by a collection of distributions P_n that are all point masses, i.e. coins each with $P_n\equiv c_n$, a constant. We call such an allocation procedure "coin-based." Now we show which sequence of point masses achieves it.

Define the *mean entropy* as :

$$\frac{1}{n}\sum_{j=1}^{n}H(c_j)=-\frac{1}{n}\sum_{j=1}^{n}[c_j\log(c_j)+(1-c_j)\log(1-c_j)].$$

Say we want to maximize $\frac{1}{n}\sum_{j=1}^{n}H(c_j)$ or, equivalently, minimize $-\frac{1}{n}\sum_{j=1}^{n}H(c_j)$ given the constraint $\frac{1}{n}\sum_{j=1}^{n}c_j=c$.

Using Lagrange multipliers we search for critical points:

$$\frac{d}{dc_j}\frac{1}{n}[c_j \log\left(c_j\right) + (1-c_j)\log(1-c_j)] = \lambda \frac{d}{dp_j}\left(\frac{1}{n}c_j\right),$$

for each c_j. This leads to:

$$\frac{1}{n}[\log\left(c_j\right) - \log(1-c_j)] = \frac{1}{n}\lambda,$$

or $\log(c_j(1-c_j)) = \lambda$) for each c_j. Since log() and $c_j/(1-c_j)$ are both one to one functions in (0,1) and λ is a constant, we must have that c_j is a constant for all *j*. Since the c_j have mean *c*, that constant must be *c*. Thus, for any allocation procedure with *n* coins, equal probabilities for each coin are required at the critical point for expected negative entropy. This must be a minimum, because the boundary points have the highest negative entropy, so the minimum cannot be there. Thus entropy is maximized there.

However, we are not done because the mean of the probabilities is usually not exactly *c*, even if it asymptotically targets *c*, and can be different for the same *n* and different allocation procedures that asymptotically target *c*.

But this can be easy resolved. Note that the maximum mean entropy for a coin based allocation procedure with mean of coins of c_m and *n* patients is just $H(c_m)$. Since the conditions require: $\lim_{n\to\infty} p_m = p$ and *H*(*x*) is continuous, it follows that maximum expected mean entropy for any such allocation procedure approaches *H*(*p*), which is the asymptotic mean entropy for a biased coin with probability *p*. This proves a) *QED*

Proof of b) i).

Assume otherwise. By Lemma 1 it must approach ρ.

Lemma 3. Then there must exist an ε, $\delta > 0$ such that:

$$\lim_{n\to\infty} P(\mid mean(P_i) - \rho \mid > \varepsilon \mid, i \le n) > \delta .$$

Proof of Lemma 3. Assume there is no such ε. Then the probability that one of the first n distributions P_j is within some small γ of ρ will be approach 1 as n approaches ∞ for any positive γ. The terms in the sequence where this does not hold will each contribute a maximum value of 1 to the variance of the first n means. Thus the variance will approach γ^2 from above for any γ, so it will approach zero, which we assumed was not true. *QED*

For any such trial, the entropy is bounded above by a trial that consists of a sequence of coins where the success probability of the i^{th} coin is equal to the mean of P_i.

Consider the subset of the treatment assignments that satisfy the conditions of Lemma 3 for some ε, $\delta > 0$ in this coin trial. Call it S. Because the means of all P_i in S are bounded away from ρ, we must have three possible scenarios:

i) There are subsequences S_1 and S_2 of S, each with positive density in S, such that all elements of S_1 are greater than $\rho + \varepsilon$ and all elements of S_2 are less than $\rho - \varepsilon$.
ii) There is a subsequence S_1 of S with positive density in S, such that all elements of S_1 are greater than $\rho + \varepsilon$ and a subsequence S_2 with positive density in the original sequence such that $S_2 > \rho$.

iii) There is a subsequence S_1 of S with positive density in S, such that all elements of S_1 are less than $\rho-\varepsilon$ and a subsequence S_2 with positive density in the original sequence such that $S_2 > \rho$.

The reason we must have one of these three possible scenarios is that the asymptotic mean of the coins is ρ, so we must have a sequence of positive density on the opposite side of ρ if there is a subsequence with positive density $>\rho+\varepsilon$ or $<\rho-\varepsilon$.

Given each of these three cases, here is how we create a sequence with the same asymptotic mean and asymptotically better entropy:

(2) Replace each of S_{1i} S_{2i}, the i^{th} elements of S_1 and S_2, with $(S_{1i}+S_{2i})/2$

It follows that the new sequence has higher entropy, because $H()$ is concave, implies

$$H\left(\frac{S_{1i}+S_{2i}}{2}\right) > \frac{1}{2}H(S_{1i})+\frac{1}{2}H(S_{2i}), \text{and}$$

$$2H\left(\frac{S_{1i}+S_{2i}}{2}\right) > H(S_{1i})+H(S_{2i}).$$

However, this does not prove that the asymptotic mean entropy is greater.

Lemma 4. The difference $2H\left(\frac{S_{1i}+S_{2i}}{2}\right) - H(S_{1i}) - H(S_{2i})$ is bounded away from zero.

First part: Fix $(S_{1i}+S_{2i})/2=\mu$. Then let $S_{1i}=\mu-k$ and $S_{2i}=\mu+k$. Start with $k=0$. Without loss of generality, let S_{2i} be closer to 0.5. As k increases, $H(S_{1i})$ will decrease more than

$H(S_{2i})$ increases, because the second derivative of H is negative. Meanwhile, $2H\left(\frac{S_{1i}+S_{2i}}{2}\right)$ is constant. Thus, the difference

$$2H\left(\frac{S_{1i}+S_{2i}}{2}\right)- H(S_{1i})-H(S_{2i})$$

is increasing as a function of k. Since $k > \varepsilon/2$, $2H((S_{1i}+S_{2i})/2)-H(S_{1i})-H(S_{2i})$ is bounded from below by:

$$Q(\mu)=2H(\mu)- H\left(\mu-\frac{1}{2}\varepsilon\right)-H\left(\mu+\frac{1}{2}\varepsilon\right).$$

Second part: $Q(u)$ is decreasing as a function of μ < 1/2, and increasing as a function of μ > 1/2.

To prove the second part, we know that $\frac{dH(\mu)}{d\mu}=-\log(\mu/(1-\mu))$. Let $k = \varepsilon/2$ It then follows that:

$$\frac{dQ(\mu)}{d\mu}=-2\log(\mu/(1-\mu))+\log\left(\frac{\mu-k}{1-\mu+k}\right)+\log(\frac{\mu+k}{1-\mu-k}),$$

which becomes:

$$-[2\log(\mu)-\log(\mu-k)-\log(\mu+k)]+[2\log(1-\mu)-\log(1-\mu+k)-\log(1-\mu-k)]$$

If $\mu = 1/2$ this derivative is clearly zero. Now note that $R(v)=2\log(v)-\log(v-k)-\log(v+k)$ is decreasing in v for $v>0$ since $R'(v)=\frac{2}{v}-\frac{1}{v-k}-\frac{1}{v+k}<0$ by convexity of $1/v$.

Thus for $\mu < 0.5$ the $Q'(\mu) < 0$ and for $\mu > 0.5$ $Q'(\mu) > 0$. Thus *Q* is minimized for the value of μ closest to 0.5, so it is always bounded away from zero for any fixed ε. Now note that $k > \varepsilon/2$. Also, $\frac{1}{2}\rho < \mu < \frac{1}{2}(1+\rho)$, so H($\mu$) is bounded away from zero. The difference

$$2H\left(\frac{S_{1i}+S_{2i}}{2}\right) - H(S_{1i}) - H(S_{2i}) > \min_{\mu}\left[2H(\mu) - H\left(\mu - \frac{\varepsilon}{2}\right) - H\left(\mu + \frac{\varepsilon}{2}\right)\right] > Q(0.5).$$

Thus Lemma 4 is proved.

Because the increases in entropy caused by the transformation (2) for each *i* are bounded away from zero over a set of positive density, this transformation increases the asymptotic mean entropy without changing the asymptotic mean, so the original sequence cannot have optimal entropy. Thus ε cannot exist, so our original assumption must be wrong. *QED*

Proof of b) ii).

We proceed by contradiction. Assume that

$$\lim_{n\to\infty} \frac{1}{n}\sum_{k=1}^{n} Var(P_k) > 0.$$

This is our original assumption.

Lemma 5: Then there exists $\varepsilon > 0$ such that

$$\lim_{n\to\infty}\frac{1}{n}\sum_{k=1}^{n} I\left(Var\left(P_k\right)>\varepsilon\right)>0$$

where $I()$ is an indicator function. In other words, the set of P_k with variance larger than ε has positive density in the infinite trial.

Proof of Lemma 5. Assume otherwise. Then we show that

$$\lim_{n\to\infty}\ \frac{1}{n}\sum_{k=1}^{n} Var(P_k)<\delta \text{ for any } \delta>0,$$

which contradicts the original assumption.

Let $\varepsilon=\delta/2$. Then we write

$$\begin{aligned}\frac{1}{n}\sum_{k=1}^{n} Var\left(P_k\right) &= \frac{1}{n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)>\varepsilon\right]Var(P_k)+\frac{1}{n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)\le\varepsilon\right]Var(P_k)\\ &< \frac{1}{4n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)>\varepsilon\right]+\frac{1}{n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)\le\varepsilon\right]Var(P_k).\end{aligned}$$

Because the maximum variance for a P_k is 1/4

$$\begin{aligned}&< \frac{1}{4}\frac{1}{n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)>\varepsilon\right]+\frac{\delta}{2}\frac{1}{n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)\le\varepsilon\right]\\ &< \frac{1}{4}\frac{1}{n}\sum_{k=1}^{n} I\left[Var\left(P_k\right)>\varepsilon\right]+\frac{\delta}{2}.\end{aligned}$$

Because of our hypothesis, the above quantity approaches $\delta/2$ in the limit. This is less than δ, so our claim is proved.

With this lemma proved, we now return to the main result. We now show that the asymptotic entropy must be less than in the optimal design. To do this we first prove Lemma 6.

Lemma 6: Take ε as in Lemma 5 and each P_i with variance > ε in Lemma 5 have mean μ_i.

Now we construct a new sequence of random variables Y_i such that $Y_i = (X_i + \mu_i)/2$. We claim:

$$E[H(Y_i)] > E[H(X_i)] + \frac{3}{4}\varepsilon.$$

Proof of Lemma 6.

$E[H(X_i)] = -E[X_i log(X_i)] - E[(1-X_i) log(1-X_i)]$. Similarly for Y_i. Now we show

(1) $$E[(1-X_i)\log(1-X_i)] > E[(1-Y_i)\log(1-Y_i)] + \frac{3}{8}\varepsilon$$

Using the fact that X_i is restricted to [0, 1], we can apply the Taylor series for $\log(1-X_i)$ to obtain

$$(1-X_i)log(1-X_i) = (1-X_i)\left(-X_i - \frac{X_i^2}{2} - \frac{X_i^3}{3} - \ldots\right) = \left(\frac{X_i^2}{2} - X_i\right) + \frac{X_i^3}{2\times 3} + \frac{X_i^4}{3\times 4} + \ldots$$

Note that $Y_i = (X_i + \mu_i)/2 = \mu_i + (X_i - \mu_i)/2$. Thus Y_i and X_i have the same mean, but Y_i is always closer to that mean than X_i. Thus Y_i is also restricted to [0, 1], and we can obtain the Taylor series:

$$(1-Y_i)log(1-Y_i) = \left(\frac{Y_i^2}{2} - Y_i\right) + \frac{Y_i^3}{2\times 3} + \frac{Y_i^4}{3\times 4} + \ldots$$

Now let v_i = Var(X_i). Then Var(Y_i) = v_i/4. Now note:

$$E[(1-X_i)log(1-X_i)]=\left(\frac{E[X_i^2]}{2}-E[X_i]\right)+\frac{E\left[X_i^3\right]}{2\times 3}+\frac{E\left[X_i^4\right]}{3\times 4}+...$$

by linearity of expectation. Similarly for Y_i . Take $k > 2$ and "k choose j" be denoted as ${}_j^kC$.

Now note:

$$E\left[Y_i^k\right]=E[(\frac{\mathrm{X_i}+\mu_i}{2})^k]=\frac{1}{2^k}E\left[\sum_{j=0}^{k}{}_j^kC\mu_i^jX_i^{k-j}\right]=\frac{1}{2^k}\left(\sum_{j=0}^{k}{}_j^kC\mu_i^jE\left[X_i^{k-j}\right]\right)$$
$$=\frac{1}{2^k}\left(\sum_{j=0}^{k}{}_j^kC(E[X_i])^jE\left[X_i^{k-j}\right]\right)<\frac{1}{2^k}\left(\sum_{j=0}^{k}{}_j^kCE\left[X_i^j\right]E\left[X_i^{k-j}\right]\right)<\frac{1}{2^k}\left(\sum_{j=0}^{k}{}_j^kCE\left[X_i^k\right]\right).$$

Here the last inequality follows from Jensen's inequality and the convexity of X_i^k on the unit interval when $(j>1)$. Because $Cov\left(X_i^j,X_i^{k-j}\right)=E\left[X_i^k\right]-E[X_i^j]E\left[X_i^{k-j}\right]$ is clearly greater than 0 on [0, 1]

$$E\left[Y_i^k\right]<\frac{E\left[X_i^k\right]}{2^k}\left(\sum_{j=0}^{k}{}_j^kC\right)=\frac{E\left[X_i^k\right]}{2^k}=2^k=E\left[X_i^k\right].$$

It then follows that $E\left[Y_i^k\right]<E\left[X_i^k\right]$, $k > 2$, and therefore that:

$$\frac{E[X_i^3]}{2\times 3}+\frac{E[X_i^4]}{3\times 4}+\ldots>\frac{E[Y_i^3]}{2\times 3}+\frac{E[Y_i^4]}{3\times 4}+\ldots$$

Because $E[X_i]=E[Y_i]$ and $Var\left(X_i\right)-Var\left(Y_i\right)=3v_i/4\geq 3\varepsilon/4$ we have

$$Var\left(X_i\right)-Var\left(Y_i\right)=E\left[X_i^2\right]-E\left[Y_i^2\right]=2[(\frac{E[X_i^2]}{2}-E[X_i])-(\frac{E[Y_i^2]}{2}-E[Y_i])]\Rightarrow$$

$$\frac{E[X_i^2]}{2}-E[X_i]-\frac{E[Y_i^2]}{2}-E[Y_i]>\frac{3}{8}\varepsilon.$$

This proves (1).

Note that by symmetry,

$$E[X_i \log(X_i)] > E[Y_i \log(Y_i)] + \frac{3}{8}\varepsilon,$$

because (1) is true for all possible P_i and we can just take $X_i = 1 - X_i'$ where X_i' is clearly also some P_i. Then we add (2) to (1) and take the negative of both sides of the equals sign, because both of these expectations are negative in the entropy formula. Thus we have:

$$E[H(Y_i)] > E[H(X_i)] + \frac{3}{4}\varepsilon.$$

Lemma 7: The sequence of expected entropies for the sequence of P_i with Var(P_i) > ε in Lemma 5 are

i) bounded away from

ii) bounded above by

the maximum expected entropy attained by a point mass at *p*, except possibly on a subsequence without positive density.

Proof: Assume i) is false. Then for all $\gamma > 0$ there exists a subsequence with positive density such that the entropies of all elements in the subsequence are within γ of that entropy attained by a point mass at *p*, denoted by $H(p)$. Choose $\gamma = \varepsilon/2$. Now we know from Part ii a) that the asymptotic variance of the means of the P_i is zero. Since the asymptotic mean of the means is *p*, we have that for any $\tau > 0$ there must exist a sub-subsequence, also with positive density (in fact, the same positive density as the subsequence), such that the means of all P_i in the sub-

subsequence lie in $(p-\tau, p+\tau)$. Without loss of generality, assume $p < 0.5$. Choose τ such that $H(p+\tau)$ is within $\varepsilon/5$ of (p). This is possible because the entropy H is a continuous function. Take X_i to be in the sub-subsequence. But then by Lemma 6, the entropy for Y_i is at least $\varepsilon/4$ greater than $H(p)$. This means its entropy must be greater than that of any point mass in $(p-\tau, p+\tau)$. But since the mean of Y_i is in the interval $(p-\tau, p+\tau)$, this leads to a contradiction, because of the earlier result about the maximum entropy P_i with a given mean being a point mass.

Assume ii) is false. Then there is a subsequence of positive density such that the asymptotic mean entropy is greater than $H(p)$. But then this subsequence must contain a sub-subsequence of positive density such that the means of the P_i in this subsequence are bounded away from p. This would lead to a contradiction. This proves Lemma 7.

We now see that if the original assumption is true, there is a subsequence of the trial that has positive density, and with mean asymptotic entropy bounded away from and above by the entropy of the optimal entropy design. Thus, if the trial is to achieve the maximal asymptotic mean entropy, there must be another subsequence of positive density with asymptotic mean entropy greater than $H(p)$. However, if this is true, this other subsequence must contain a sub-subsequence with means of the P_i in this sub-subsequence are bounded away from *p*. However, this would lead to a contradiction *QED*

Now we prove the other direction of the Optimal Entropy Theorem. Assume the two conditions hold. Then for all ε, $\delta > 0$ there exists N such that for any $n > N$ the area of the P_i in $(\rho-\varepsilon, \rho+\varepsilon)$ is greater than $1-\delta$. This is due to Chebyshev's inequality. Then it follows that

$$E[H(P_i)] > (1-\delta)\min\left[H(\rho-\varepsilon), H(\rho+\varepsilon)\right],$$

because $H()$ is concave. Also, for $\rho \neq 1/2$,

$$E[H(P(n))] < \max\left[H(\rho-\varepsilon), H(\rho+\varepsilon)\right],$$

for ε sufficiently small. Thus as $\varepsilon, \delta \to 0$,

or as $N \to \infty$, $E[H(P_i)] \to H(\rho)$ if $\rho \neq 1/2$. If $\rho = 1/2$ then this still holds because

$$(1-\delta)\min(H(\rho-\epsilon), H(\rho+\epsilon)) < E[H(P_i)] < H(1/2).$$

Thus, the maximum asymptotic mean entropy is achieved for any such design. *QED*

Proof of Theorem 2, Part i).

Break $\{P_{n_k}\}$ into two subsequences, one where $E(P_{n_{kj}} - \rho) > \varepsilon$ and one where $E(P_{n_{k\ell}} - \rho) < -\varepsilon$. At least one of these subsequences must be infinite. WLOG assume it is $\{P_{n_{kj}}\}$, the first subsequence. Then for each $P_{n_{kj}}$, the density of $P_{n_{kj}} - \rho$ must gave positive probability on the interval $[\varepsilon/2, 1-\rho]$, since if it did not, $E(P_{n_{kj}} - \rho) < \varepsilon/2 < \varepsilon$, a contradiction. Moreover, this positive probability is bounded from below for all n_{kj} by a quantity satisfying: $\frac{1}{2}\varepsilon(1-p_b) + (1-\rho)(p_b) > \varepsilon$, therefore

$$-\frac{1}{2}\varepsilon p_b + p_b - \rho p_b > \frac{1}{2}\varepsilon \;\Rightarrow p_b > \frac{\frac{1}{2}\varepsilon}{1-\rho-\frac{1}{2}\varepsilon} > 0.$$

Let $F_{S^P_{n_{k_j}}}$ be the cdf of $\sqrt{n}(P_{n_{k_j}} - \rho)$. Then $1 - F_{S^P_{n_{k_j}}}(\sqrt{n}\frac{1}{2}\varepsilon) > p_b$ for any *n*.

Since $\sqrt{n}\frac{1}{2}\varepsilon$ is unbounded, it becomes impossible $S^P_{n_{k_j}}$ for to have a $N(0,\sigma^2)$ attractor distribution, which is a contradiction. ∴

Thus, we see that $E(P_n - \rho) \to 0$ and therefore $E(P_n) \to \rho$, which satisfies the first condition of the Optimal Entropy Theorem.

Lemma 8: $\lim_{n\to\infty} Var(P_n) \to 0$

Proof of Lemma 8.

$Var(P_n) = Var(P_n - \rho)$ and $P_n - \rho$ has support only in $[-\rho, 1-\rho]$. We proceed by contradiction. Suppose that $Var(P_n)$ does not approach zero. The $Var(P_n - \rho)$ does not approach zero, so there must be some $\varepsilon > 0$ and infinite subsequence P_{n_k} such that $Var(P_{n_k} - \rho) > \varepsilon$ for any n_k.

By Lemma 8 there exists *m* such that $|E[P_{n_k}] - \rho| < \frac{1}{4}\sqrt{\varepsilon}$. Then for each $P_{n_k} - \rho$ the density of P_{n_k} must have positive probability in the set

$$[-\rho, 1-\rho] \setminus \left[\rho - \frac{3}{4}\sqrt{\varepsilon}, \rho + \frac{3}{4}\sqrt{\varepsilon}\right].$$

Thus must always have positive probability on $x > \frac{3}{4}\sqrt{n\varepsilon}$, which is unbounded. Thus S^P_n cannot approach $N(0,\sigma^2)$ in distribution, which is a contradiction. ∴

Since both conditions of the Optimal Entropy Theorem are satisfied, S_n^P mush have asymptotic optimal entropy. The proof for S_n^Q is the same.

Proof of Theorem 2, Part ii).

Let the sequence of random variables R_n be defined as:

$$R_n = \frac{\sigma}{\tau}(Q_n - \rho) + \rho .$$

Then we see that:

$$\sqrt{n}(R_n - \rho) = \sqrt{n}\frac{\sigma}{\tau}(Q_n - \rho) \underset{D}{\rightarrow} N(0, \sigma^2) .$$

Let $S_n^P = \sqrt{n}(P_n - \rho)$, $S_n^Q = \sqrt{n}(Q_n - \rho)$ and $S_n^R = \sqrt{n}(R_n - \rho)$.

Clearly the sequence of random variables $\{B_k\} = S_1^P, S_1^R, S_2^P, S_2^R, S_3^P, S_3^R, \ldots$ converges in distribution to $N(0, \sigma^2)$. By the Skorohod Representation Theorem, we know that there is a sequence $\{T_k\}$ such that:

i) Each random variable T_k has the same distribution as each B_k

ii) $T_k \underset{P}{\rightarrow} X \sim N(0, \sigma^2)$

Now note that as $k \rightarrow \infty$

$$S_k^R - S_k^P = T_{2k-1} - T_{2k} = (T_{2k-1} - X) - (T_{2k} - X) = op(1) - op(1) = op(1)$$

because $T_k \underset{P}{\rightarrow} X$. Here $y=op(x)$ if y/x approaches 0 in probability. Thus

$$S_k^R = S_k^P + op(1) \Rightarrow \sqrt{n}(R_n - \rho) = \sqrt{n}(P_n - \rho) + op(1)$$
$$\Rightarrow R_n - \rho = P_n - \rho + op(\frac{1}{\sqrt{n}})$$
$$\Rightarrow R_n = P_n + op(\frac{1}{\sqrt{n}}).$$

Lemma 9: If we have:

i) $\{A_n\},\{B_n\}$ are sequences of random variables with support on [0,1]

ii) $A_n = B_n + op(\omega_n)$

iii) ω_n is a random variable such that $\omega_n \equiv n^{-\alpha}$ and $\alpha > 0$ is a constant

iv) A_n, B_n are bounded away from zero in probability

Then $H(A_n) = H(B_n) + op(\omega_n)$, where $H()$ means entropy.

Proof of Lemma 9.

First, we establish that: $H(|x-y|) \rhd |H(x) - H(y)|$. If $x,y > 1/2$ or $x,y < 1/2$, then this statement follows from the concavity of $H()$. Now assume otherwise. Without loss of generality let $x < y$. If $y - x < 1/2$ then the statement again follows from the concavity of $H()$. If $y - x \geq 1/2$ then $y - x$ is closer to 1/2 than either y or x, so the desired result follows. By the Continuous Mapping Theorem, $H(op(1)) = op(1)$. By the power series for $H()$, $n^{\alpha} op(\omega_n) = op(\log(n))$. Thus $H(|A_n - B_n|) = op(\log(n)/n^{\alpha})$. Because A_n, B_n are bounded away from zero in probability,

$\left[H(A_n)-H(B_n)\right]/H(A_n-B_n)$ is $op(1/\log(n))$ due to the value of the derivative of the entropy function. Thus $H(A_n)=H(B_n)+op(1/n^{\alpha})$. This is the definition of $H(A_n)=H(B_n)+op(\omega_n)$ $\therefore$

Let $\alpha=-1/2$. It then follows from Lemma 9 that $H(R_n)=H(P_n)+op(1/\sqrt{n})$.

Now we proceed in a manner similar to the proof of the Optimal Entropy Theorem.

$$R_n=\frac{\sigma}{\tau}(Q_n-\rho)+\rho=\frac{\sigma}{\tau}Q_n+(1-\frac{\sigma}{\tau})\rho\Rightarrow$$

$$E[(R_n)^k]=E[(\frac{\sigma}{\tau}Q_n+(1-\frac{\sigma}{\tau})\rho)^k]$$

$$=E[\sum_{i=0}^{k}\frac{k!}{i!(k-i)!}(\frac{\sigma}{\tau}Q_n)^i((1-\frac{\sigma}{\tau})\rho)^{k-i}]$$

$$=\sum_{i=0}^{k}\frac{k!}{i!(k-i)!}(\frac{\sigma}{\tau})^i(1-\frac{\sigma}{\tau})^{k-i}E[Q_n{}^i\rho^{k-i}]$$

$$\le\sum_{i=0}^{k}\frac{k!}{i!(k-i)!}(\frac{\sigma}{\tau})^i(1-\frac{\sigma}{\tau})^{k-i}E[Q_n{}^i]E[Q_n{}^{k-i}],$$

by Jensen's inequality since $E[Q_n]=\rho\ge 0$

$$\le\sum_{i=0}^{k}\frac{k!}{i!(k-i)!}(\frac{\sigma}{\tau})^i(1-\frac{\sigma}{\tau})^{k-i}E[Q_n{}^k].$$

Since $Q_n{}^i$, $Q_n{}^{k-i}$ have positive covariance, is equal to $E[Q_n{}^k]$.

We know from power series that:

$$(1-Q_n)\log(1-Q_n)=(\frac{Q_n^2}{2}-Q_n)+\frac{Q_n^3}{2\times 3}+\frac{Q_n^4}{3\times 4}+\ldots$$

And similarly for R_n .Thus since $E[Q_n] = E[R_n]$ and $E[Q_n{}^k] \geq E[R_n{}^k]$:

$$E[(1-Q_n)\log(1-Q_n)] - E[(1-R_n)\log(1-R_n)] \geq E[(\frac{Q_n^2}{2} - Q_n)] - E[(\frac{R_n^2}{2} - R_n)]$$
$$= \frac{1}{2}(Var(Q_n) - Var(R_n)),$$

hence $E[H(Q_n)] < E[H(R_n)] - (Var(Q_n) - Var(R_n))$, by the symmetry argument used in the proof of the Optimal Entropy Theorem.

Because of the moment condition in the statement of the theorem, we know that the random variables converge to τ^2 and σ^2 respectively. Thus there exists $m \in \mathrm{N}$ such that

$$Var(S_j^Q) - Var(S_j^R) > \frac{\tau^2 - \sigma^2}{2} \text{ for any } j > m$$
$$\Rightarrow Var(Q_j) - Var(R_j) > \frac{\tau^2 - \sigma^2}{2\sqrt{n}} \text{ for any } j > m.$$

Hence for any $b > m$,

$$\sum_{n=m+1}^{q} E[H(Q_n)] < \sum_{n=m+1}^{q} E[H(R_n)] - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=m+1}^{q} \frac{1}{\sqrt{n}}.$$

As $q \to \infty$ $\sum_{n=m+1}^{q} \frac{1}{\sqrt{n}}$ diverges, so we have for any $q > c \in N$

$$\sum_{n=1}^{q} E[H(Q_n)] < \sum_{n=1}^{q} E[H(R_n)] - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=1}^{q} \frac{1}{\sqrt{n}}$$
$$\sum_{n=1}^{q} E[H(Q_n)] < \sum_{n=1}^{q} E[H(P_n)] + \sum_{n=1}^{q} E[op(\frac{1}{\sqrt{n}})] - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=1}^{q} \frac{1}{\sqrt{n}}.$$

P_n and R_n each only have support on [0,1]. So the $op(\frac{1}{\sqrt{n}})$ random variable only has support on [-1,2]. Now we have the following lemma:

Lemma 10: Let ω be a sequence of random variables with support on [-1,2] such that $\omega = op(\frac{1}{\sqrt{n}})$. Then the sequence of random variables $\varphi = E[\omega]$ is also $op(\frac{1}{\sqrt{n}})$.

Proof of Lemma 10.

For any $\varepsilon,\ \delta < 1$ and $b \in N$ such that for any $n > b$,

(1) $\Pr\left[\frac{|\omega_n|}{1/\sqrt{n}} < \varepsilon\right] > 1-\delta$, therefore $\left|E\left(\frac{\omega_n}{1/\sqrt{n}}\right)\right| < (1-\delta)\varepsilon + 2\delta$ because ε and 2 are the most extreme values. Hence

$$|E[\omega_n]| < \frac{1}{\sqrt{n}}[((1-\delta)\varepsilon + 2\delta)] < \frac{3}{\sqrt{n}}\max(\delta,\varepsilon).$$

Also $|E[\omega_n]| < \frac{3}{\sqrt{n}}\max^*(\delta,\varepsilon)$, where $\max(\delta,\varepsilon) = \inf(\max(\delta,\varepsilon))$ over all δ,ε where (1) holds.

As $n \to \infty$ $\max^*(\delta,\varepsilon) \to 0$ so,

$$\left|\frac{E[\omega_n]}{1/\sqrt{n}}\right| < 3\max(\delta,\varepsilon) \to 0 .$$

So

$$\frac{E[\omega_n]}{1/\sqrt{n}} \underset{P}{\to} 0,\ \varphi \text{ is } op(\frac{1}{\sqrt{n}}) \therefore$$

Returning to the previous sum we have for any $q > c \in N$:

$$\sum_{n=1}^{q} E[H(Q_n)] < \sum_{n=1}^{q} E[H(P_n)] + \sum_{n=1}^{q} E[op(\frac{1}{\sqrt{n}})] - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=1}^{q} \frac{1}{\sqrt{n}},$$

which becomes after Lemma 10:

$$\sum_{n=1}^{q} E[H(Q_n)] < \sum_{n=1}^{q} E[H(P_n)] + \sum_{n=1}^{q} op(\frac{1}{\sqrt{n}}) - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=1}^{q} \frac{1}{\sqrt{n}}.$$

Where $op(\frac{1}{\sqrt{n}})$ denotes a point mass $op(\frac{1}{\sqrt{n}})$ random variable.

Then there exists $g \in N$ such that for any $n > g$,

$$\frac{op(\frac{1}{\sqrt{n}})}{\frac{1}{\sqrt{n}}} < \frac{1}{2}.$$

Thus for $d \in \mathrm{N}, d > g$:

$$\sum_{n=g+1}^{d} op(\frac{1}{\sqrt{n}}) - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=g+1}^{d} \frac{1}{\sqrt{n}} < \sum_{n=g+1}^{d} -\frac{1}{2\sqrt{n}}.$$

Since $\sum_{n=1}^{g} op(\frac{1}{\sqrt{n}}) - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=1}^{g} \frac{1}{\sqrt{n}}$ is finite, let it equal the constant F_c. Then

$$\sum_{n=1}^{d} op(\frac{1}{\sqrt{n}}) - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=1}^{d} \frac{1}{\sqrt{n}} = \sum_{n=g+1}^{d} op(\frac{1}{\sqrt{n}}) - (\frac{\tau^2 - \sigma^2}{2}) \sum_{n=g+1}^{d} \frac{1}{\sqrt{n}} + F_c < \sum_{n=g+1}^{d} -\frac{1}{2\sqrt{n}} + F_c.$$

Then

$$\sum_{n=1}^{d} op(\frac{1}{\sqrt{n}}) - \frac{\tau^2 - \sigma^2}{2} \sum_{n=1}^{d} \frac{1}{\sqrt{n}} = \sum_{n=g+1}^{d} op(\frac{1}{\sqrt{n}}) - \frac{\tau^2 - \sigma^2}{2} \sum_{n=g+1}^{d} \frac{1}{\sqrt{n}} + F_c < \sum_{n=g+1}^{d} -\frac{1}{2\sqrt{n}} + F_c.$$

As *d* increases, this final sum eventually becomes negative, since diverges. It stays negative. Thus for all *d* greater than some $d_1 \in \mathrm{N}$ we have:

$$\sum_{n=1}^{d} E[H(Q_n)] < \sum_{n=1}^{d} E[H(P_n)] + \theta_n,$$

where $\theta_n < 0$. Hence $\frac{1}{d}\sum_{n=1}^{d} E[H(Q_n)] < \frac{1}{d}\sum_{n=1}^{d} E[H(P_n)]$. Which means the entropy of patients in the first trial permanently exceeds that of the second. *QED*